ISSN 0003-2999
Volume 72, Number 3, March 1991

40

Anesthesia and Analgesia

V. 72
3-4
1991

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

P, 24,544

CUe -H02986-40-P024544

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron* is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral erve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle elaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

enal Failure: Norcuron* is well tolerated without clinically significant prolongation of neuromuscular blocking effect in tients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric ents some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-ive surgery, a lower initial dose of Norcuron* should be considered.

ed Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous s resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be ased.

lic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping the role the liver plays in Norcuron* metabolism and excretion. Data currently available do not permit dosage mmendations in patients with impaired liver function.

g-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate echanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as orcuron*.

alignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially al hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron*, the administration of Norcuron* should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron* before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron*, therefore these drugs and Norcuron* may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron* will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron* may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron*. Norcuron* should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron* was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron* as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron* is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron* produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron* as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol* (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron*. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron* (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron* by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron* is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron* is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron*. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron* to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron* are recommended; after the initial Norcuron* injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron* lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron* should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron* should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron* infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron* can be prepared by mixing Norcuron* with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron* can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

10 mg of Norcuron in 100 mL solution
†20 mg of Norcuron* in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON* INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
µg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron* is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

References:

1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983;58:438-440.
2. Lowry KG, Mirakhur RK, Lavery GG, et al: Vecuronium and atracurium in the elderly: A clinical comparison with pancuronium. *Acta Anaesthesiol Scand* 1985;29:405-408.
3. Miller RD, Rupp SM, Fahey MR, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron*. Amsterdam, Excerpta Medica, 1983, pp 124-126.
4. Bell CF, Hunter JM, Jones RS, et al: Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985;57:160-168

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Manufactured for ORGANON INC.
By BEN VENUE LABORATORIES, INC. • BEDFORD, OHIO 44146
or by
ORGANON INC. • WEST ORANGE, NEW JERSEY 07052

PTD. IN USA-440, 441

©1989 ORGANON INC.

5310117

2001

THE FUTURE IS HERE TODAY!

The Most Powerful Critical Care Syringe Infusion Pump Available.

- Automatically programs the syringe size
- Microprocessor calibrated occlusion alarm
- Uses all syringe sizes (1ml - 60ml)
- Programmable volume limit with KVO feature
- Total accumulated volume readout
- Back lit display for easy night reading
- Small and lightweight
- Blood, Lipid, Antibiotic and other drug infusions

medfusion inc
A medex inc company

3450 River Green Court
Duluth, Georgia 30136, (USA)
404-623-9809 800-358-6019

Anesthesia and Analgesia

Official Journal of the International Anesthesia Research Society

Editor-in-Chief
Ronald D. Miller, MD
San Francisco, California

Associate Editor-in-Chief
John H. Tinker, MD
Iowa City, Iowa

Editorial Board

David R. Bevan, MA, MB, BChir
Montreal, Quebec, Canada

Thomas J. Gal, MD
Charlottesville, Virginia

Edward D. Miller, Jr, MD
New York, New York

Nathan L. Pace, MD
Salt Lake City, Utah

Richard J. Palahniuk, MD
Minneapolis, Minnesota

John Savarese, MD
New York, New York

Walter S. Nimmo, MD, BSc, FRCP, FFARCS
Edinburgh, Scotland

Section Editors

Cardiovascular Anesthesia
Joseph G. Reves, MD, Durham, North Carolina

Ambulatory Anesthesia
Patricia Kapur, MD, Los Angeles, California

Neurosurgical Anesthesia
Donald S. Prough, MD, Winston-Salem, North Carolina

Obstetrical Anesthesia
Mieczyslaw Finster, MD, New York, New York

Regional Anesthesia and Pain Management
Phillip O. Bridenbaugh, MD, Cincinnati, Ohio

Pediatric Anesthesia
Paul R. Hickey, MD, Boston, Massachusetts

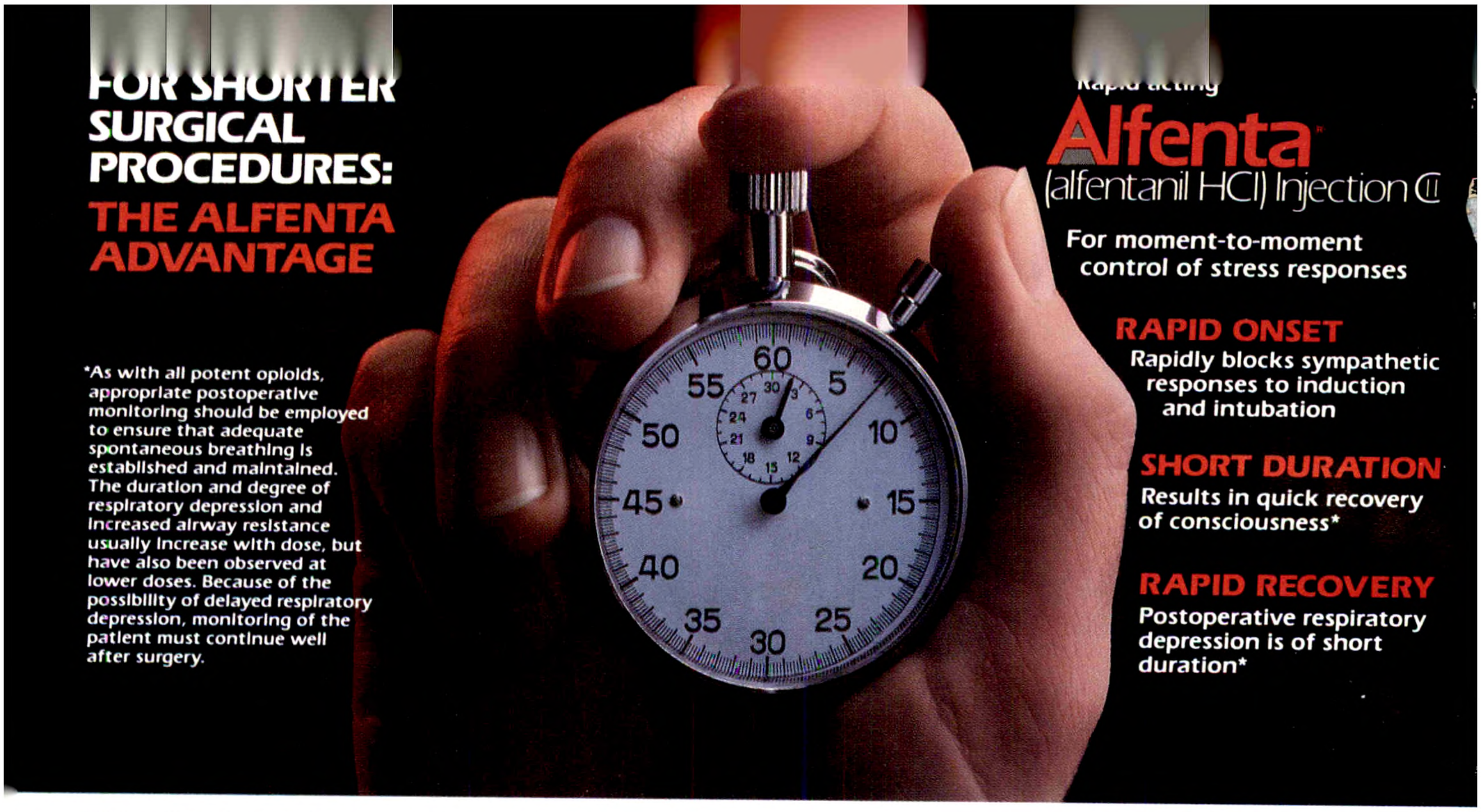
Critical Care
Ronald G. Pearl, MD, PhD, Stanford, California

Book Review Editor
Norig Ellison, MD, Philadelphia, Pennsylvania

Managing Editor
King Kryger, PhD

Manuscripts should be addressed to: Ronald D. Miller, MD, Editor-in-Chief, *Anesthesia and Analgesia*, University of California, San Francisco, 521 Parnassus Avenue, Room C-450, San Francisco, CA 94143-0648. **Editorial correspondence** should be addressed to: King Kryger, PhD, Managing Editor, *Anesthesia and Analgesia*, 3497 Sacramento Street, San Francisco, CA 94118 [telephone: (415) 292-7964; FAX: (415) 292-5157]. For information concerning preparation of manuscripts, see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to: Book Review Editor, Norig Ellison, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.



*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA

Piscataway, N.J. 08854

March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

© Janssen Pharmaceutica Inc. 1989 JPI-AL-040A

Anesthesia and Analgesia

LIBRARY

Contents

Volume 72, Number 3, March 1991

SCIENTIFIC ARTICLES

Cauda Equina Syndrome After Continuous Spinal Anesthesia — *Mark L. Rigler, Kenneth Drasner, Tom C. Krejcie, Sharon J. Yelich, Faith T. Scholnick, James DeFontes, and David Bohner* — 275

Should You Cancel the Operation When a Child Has an Upper Respiratory Tract Infection? — *Marsha M. Cohen and Cal B. Cameron* — 282

Influence of Desflurane on Regional Distribution of Coronary Blood Flow in a Chronically Instrumented Canine Model of Multivessel Coronary Artery Obstruction — *J. Craig Hartman, Paul S. Pagel, John P. Kampine, William T. Schmeling, and David C. Warltier* — 289

Continuous Postoperative Regional Analgesia by Nerve Sheath Block for Amputation Surgery—A Pilot Study — *Allan Fisher and Yitzhak Meller* — 300

Patient-Controlled Sedation During Epidural Anesthesia — *Woo Young Park and Patricia A. Watkins* — 304

Role of Experience in the Response to Simulated Critical Incidents — *Abe DeAnda and David M. Gaba* — 308

Comparison of Kinetics of Sevoflurane and Isoflurane in Humans — *Nobuhiko Yasuda, Stephen H. Lockhart, Edmond I. Eger II, Richard B. Weiskopf, Jin Liu, Michael Laster, Shahram Taheri, and Natalie A. Peterson* — 316

Low-Dose Clonidine Enhances Pregnancy-Induced Analgesia to Visceral but Not Somatic Stimuli in Rats — *Hiroshi Iwasaki, J. G. Collins, Yoji Saito, Hiroshi Uchida, and Ann Kerman-Hinds* — 325

Multiple-Dose Evaluation of Intravenous Hydromorphone Pharmacokinetics in Normal Human Subjects — *Harlan F. Hill, Barbara A. Coda, Akira Tanaka, and Randy Schaffer* — 330

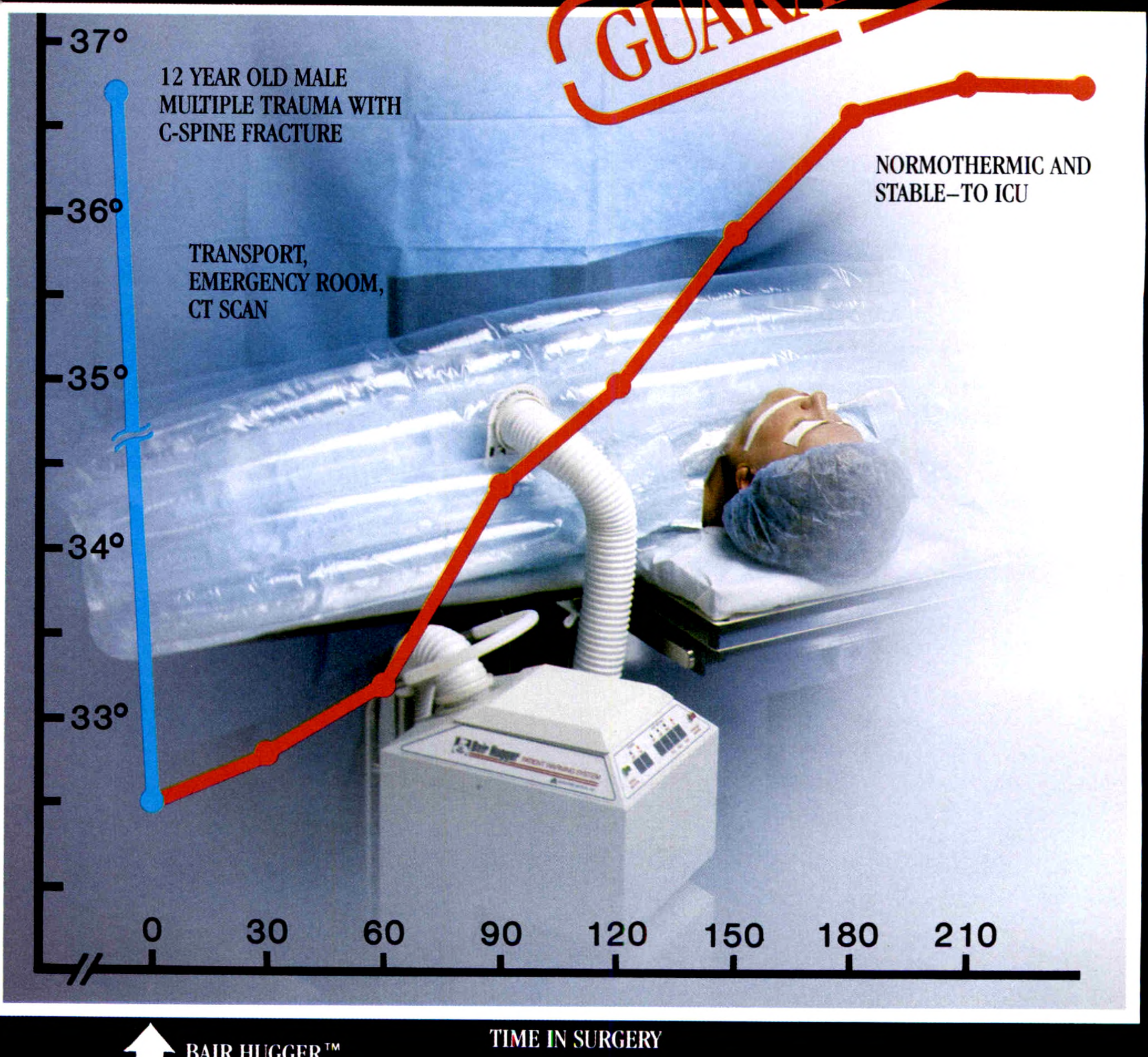
Low-Dose Bupivacaine Does Not Improve Postoperative Epidural Fentanyl Analgesia in Orthopedic Patients — *Neal H. Badner, Eleanor J. Reimer, Wendy E. Komar, and Carol A. Moote* — 337

Long-Latency Auditory Evoked Potentials During General Anesthesia: N1 and P3 Components — *G. Plourde and T. W. Picton* — 342

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. *© 1991 by the International Anesthesia Research Society.* *Second class postage paid at New York, NY and at additional mailing offices. Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year; in all other countries, $110.00. (See General Information in this issue for further details regarding membership.) Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico; $55.00 for surface airlift to Europe; $75.00 for surface airlift to Japan; and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: Anesthesia and Analgesia, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.*

NORMOTHERMIA IN THE O.R.

GUARANTEED*



BAIR HUGGER™
CONVECTIVE WARMING™
THERAPY STARTED

*Terms of guarantee:

1. Bair Hugger™ Convective Warming Therapy must begin immediately after induction of anesthesia on the "high" setting and continue throughout the case if indicated.

2. Infused blood and fluids must be warmed to body temperature.

If these two criteria are met and the patient is hypothermic at the end of the operation (core temperature < 36°C). Augustine Medical will replace the Warming Cover. This guarantee is limited to the replacement of the Warming Cover.

For more information
about Bair Hugger™
Convective Warming Therapy,
call 1-800-733-7775
or (612) 941-8866

AUGUSTINE MEDICAL INC.

PRACTICAL SOLUTIONS TO COMMON PROBLEMS IN ACUTE CARE™

10393 West 70th Street • Eden Prairie, Minnesota 55344

SCIENTIFIC ARTICLES—*continued*

Vagal Involvement in the Action of Exogenous Adenosine Triphosphate on Reflex Renal Sympathetic Nerve Activity — *Chikuni Taneyama, Hiroshi Goto, Kirk T. Benson, Gregory K. Unruh, and Kasumi Arakawa* 351

Effects of Fentanyl, Sufentanil, and Alfentanil on Brain Retractor Pressure — *Ian A. Herrick, Adrian W. Gelb, Pirjo H. Manninen, Howard Reichman, and Steven Lownie* 359

Effects of Succinylcholine on the Pharmacodynamics of Pipecuronium and Pancuronium — *Michel Y. Dubois, Neal W. Fleming, and Dawn E. Lea* 364

Effect of Ranitidine on Bupivacaine Disposition — *Wayne T. Brashear, Kathy J. Zuspan, Noam Lazebnik, Betty R. Kuhnert, and Leon I. Mann* 369

Effect of Fentanyl and Nitrous Oxide on the Desflurane Anesthetic Requirement — *Ahmed F. Ghouri and Paul F. White* 377

HISTORICAL ARTICLE

Gardner Quincy Colton: Pioneer of Nitrous Oxide Anesthesia — *Gary B. Smith and Nicholas P. Hirsch* 382

CLINICAL REPORTS

Blind Nasal Intubation With Audio-Capnometry — *Sota Omoigui, Peter Glass, Dave L. J. Martel, Kenneth Watkins, Kent L. Williams, Sherry M. Whitefield, and Larry L. Wooten* 392

Onset of Amputation Stump Pain Associated With Epidural Anesthesia — *Eisso R. Bulder and Willem L. H. Smelt* 394

Speedballs: A New Cause of Intraoperative Tachycardia and Hypertension — *Jon Samuels, Steven S. Schwalbe, and Gertie F. Marx* 397

Are Breech Deliveries an Indication for Lumbar Epidural Analgesia? — *Andre Van Zundert, Leo Vaes, Maurice Soetens, Marc De Vel, Paul Van Der Aa, Agnes Van Der Donck, Herman Meeuwis, and Francis Smolders* 399

Nightmares and Recovery From Anesthesia — *D. Suresh* 404

LETTERS TO THE EDITOR

The Importance of Documenting Complete Sympathetic Blockade — *Brian D. Smith and James J. Gibbons* 406

A "Loading Port" for Syringe Infusion Pumps — *Richard P. O'Flynn and Janet N. Siler* 407

Are the Hemodynamic Effects of Dexmedetomidine Influenced by the Background Anesthetic? — *Mark S. Scheller and Mark H. Zornow* 408

In Response — *Bente R. Karlsson and Petter A. Steen* 408

Harold Griffith and John Snow — *Richard I. Bodman* 409

If You're Looking For The Best Anesthesiology Billing and Practice Management System, We've Got Your Number.

1-800-2GET-NHS

Call us today, and we'll send you a free information kit on the best computer system designed exclusively for anesthesiologists —The ULTRA Anesthesiology Billing and Practice Management System from Northern Health Systems.

You'll receive all of the information you need to automate your growing practice.

Information that will improve the efficiency of your office and speed your cash flow.

You'll discover a feature-packed system that can give you instant patient information. Simplify your accounting. Process your claims electronically. Produce customized reports. And much, much more.

Call us toll-free at 1-800-2GET-NHS for your free information kit. It's the only number you need.

NHS Northern Health Systems, Inc.
5500 Corporate Drive, Pittsburgh, PA 15237

LETTERS TO THE EDITOR—*continued*

Severe Hypocapnia During Cardiopulmonary Bypass — *Mark E. Romanoff and Philip W. Kocoloski* 410

β-Adrenergic Receptor Function in Surgical Patients — *Debra A. Schwinn* 412

In Response — *Jean Marty and Martin Nimier* 412

A History of Nurse Anesthesia? — *Douglas R. Bacon* 412

Intraspinal Opiates in Patients Receiving Podophyllum — *W. Thomas Edwards* 413

Propofol Does Not Trigger Malignant Hyperthermia — *Jonathan S. Gallen* 413

Oral Pulse Oximetry in Small Children — *Guillermo E. Lema* 414

Why 70 Watts to Evaluate Metal Tapes for CO_2 Laser Surgery? — *R. Williamson* 414

In Response — *Mitchel B. Sosis* 415

Systemic Droperidol and Epidural Morphine in the Management of Postoperative Pain — *José Carlos Almeida Carvalho, Roberto Simão Mathias, Waldir Garcia Senra, Marcelo Luis Abramides Torres, Constantin Adam, Alberto Vasconcelos, José Edison de Moraes, and Sonia Regina Corrallo* 416

BOOK REVIEWS

Obstetric Anesthesia. By L. S. Reisner, ed. — *Maya S. Suresh* 417

Fiberoptic Airway Endoscopy in Anesthesia and Critical Care. By Andranik Ovassapian — *Howard L. Zauder* 417

Envisioning Information. By Edward R. Tufte — *Mark S. Schreiner* 418

Postanesthesia Care Unit Problems. By G. Shapiro, ed. — *David J. Cullen* 418

Clinical Applications of Ventilatory Support. By R. R. Kirby, M. J. Banner, and J. B. Downs, eds. — *M. Christine Stock* 420

Books Received 420

GENERAL INFORMATION

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 by the International Anesthesia Research Society. Second class postage paid at New York, NY and at additional mailing offices.

Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year; in all other countries, $110.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. Associate Membership is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). Educational Membership (half the full-member price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2-, 3-, or 4-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, OH 44131-2553.

Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico; $55.00 for surface airlift to Europe; $75.00 for surface airlift to Japan; and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Single issues: Single copy information is available from Elsevier Science Publishing Co., Inc., upon request. Back volume (all issues prior to 1983) information is available from the IARS.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc., 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence, or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See Classified Ads section for submission of classified ad material.

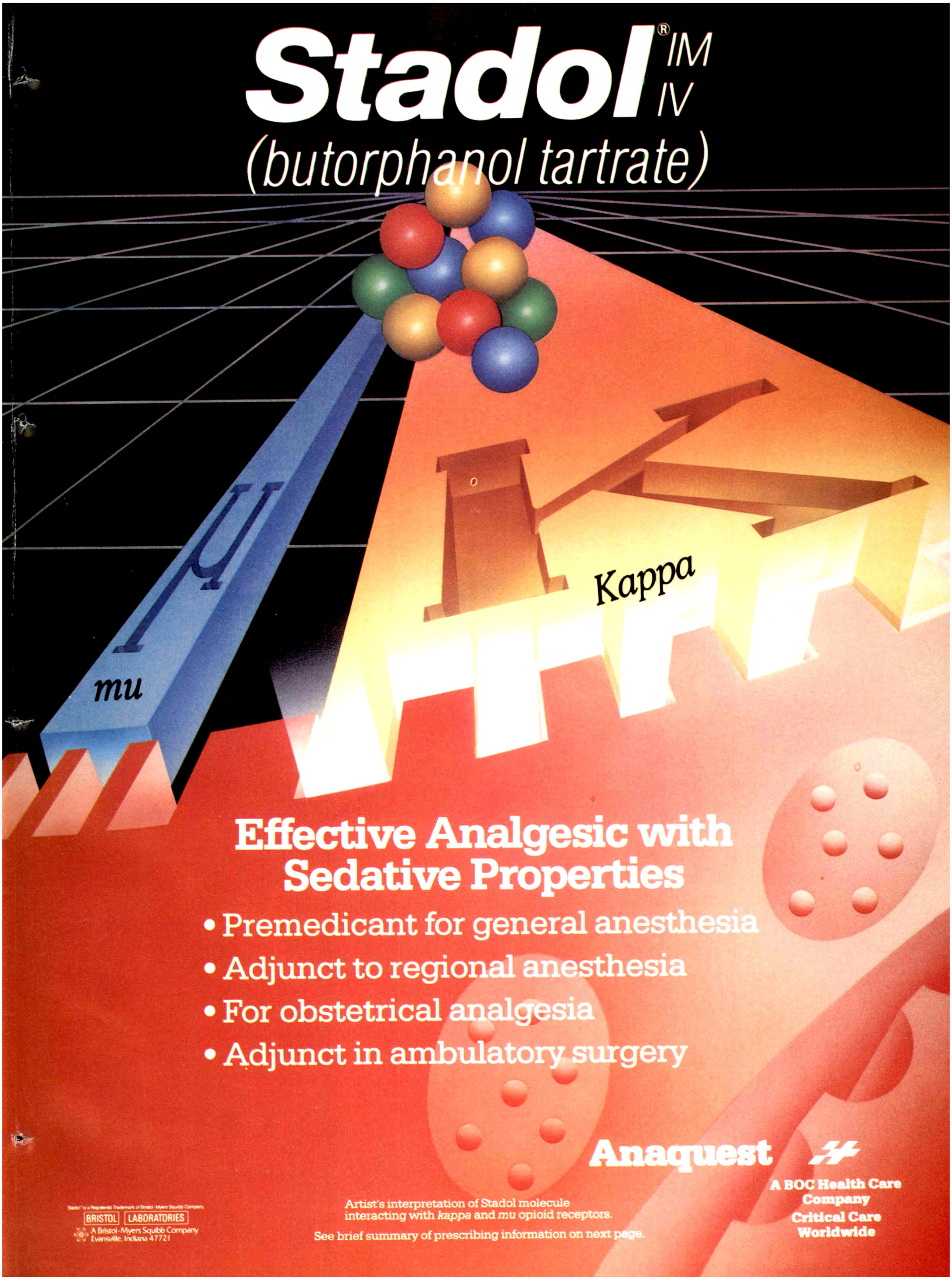
All articles published in this journal become the property of the International Anesthesia Research Society. This journal has been registered with the Copyright Clearance Center, Inc. Consent is given for the copying of articles for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay through the center the per copy fee stated in the code on the first page of each article for copying beyond that permitted by the US Copyright Law. If no code appears on an article, the author has not given broad consent to copy, and permission to copy must be obtained directly from the author. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) are processed through Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Prices are provided upon request.

This journal is abstracted/indexed in: Biological Abstracts, Chemical Abstracts, Current Contents/Life Sciences, Current Contents/Clinical Practice, Excerpta Medica, Index Medicus, ISI/Biomed, and Science Citation Index.

On line text is available through BRS Colleague, 8000 Westpark Drive, McLean, VA 22102. Telephone: (800) 289-4277.

This journal is printed on acid-free paper.



Stadol® IM IV

(butorphanol tartrate)

Effective Analgesic with Sedative Properties

- Premedicant for general anesthesia
- Adjunct to regional anesthesia
- For obstetrical analgesia
- Adjunct in ambulatory surgery

Anaquest

A BOC Health Care Company
Critical Care Worldwide

Artist's interpretation of Stadol molecule interacting with *kappa* and *mu* opioid receptors.

See brief summary of prescribing information on next page.

Stadol® is a Registered Trademark of Bristol-Myers Squibb Company

BRISTOL LABORATORIES
A Bristol-Myers Squibb Company
Evansville, Indiana 47721

Stadol® *(butorphanol tartrate)*

For complete information consult official package circular.

INDICATIONS AND USAGE

Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS

Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS

Patients Physically Dependent on Narcotics

Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia

Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence

Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure

Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects

Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS

Certain Respiratory Conditions

Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function

Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery

Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication

Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy

The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human does.

Usage in Labor and Delivery

In general, the safety to the mother and fetus following the administration of Stadol during labor has been established, however, there have been a few reports of infant respiratory distress/apnea occurring after delivery (less than 1%; see Adverse Reactions). Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers

The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children

Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS

The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: Vomiting

Respiratory: slowing of respiration, shallow breathing, apnea

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE

Manifestations

Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment

The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY

Stadol (butorphanol tartrate Inj., USP) for I.M. or I.V. use is available as follows:

NDC 0015-5644-20 - 2 mg per mL, 2-mL vial
NDC 0015-5645-20 - 1 mg per mL, 1-mL vial
NDC 0015-5646-20 - 2 mg per mL, 1-mL vial
NDC 0015-5648-20 - 2 mg per mL, 10-mL multi-dose vial

For information on package sizes available, refer to the current price schedule.

BRISTOL LABORATORIES
Bristol-Myers
U.S. Pharmaceutical and Nutritional Group
Evansville, Indiana 47721

HALOTHANE U.S.P.

Produced by Halocarbon Laboratories

NDC 12164-001-25
Halothane U.S.P.
250 ml
2-Bromo-2-chloro-1, 1, 1-trifluoroethane
Contains 0.01% Thymol
FOR INHALATION ANESTHESIA
See Accompanying Literature
NONFLAMMABLE • NONEXPLOSIVE
KEEP BOTTLE SECURELY CLOSED
AVOID EXCESSIVE HEAT
CAUTION: FEDERAL LAW (U.S.A.) PROHIBITS DISPENSING WITHOUT PRESCRIPTION
Manufactured in U.S.A. by
HALOCARBON LABORATORIES
U.S. Highway 1 and Revco Rd.
N. Augusta, S.C. 29841
EXP. DATE: SEP 1994

When requested
bottle comes
with collar.

- First maker of fluorinated anesthetics in the U.S.A.
- Pioneer in anesthetic purity
- Lowest price of any potent anesthetic

HALOCARBON
LABORATORIES
A division of Halocarbon Products Corporation

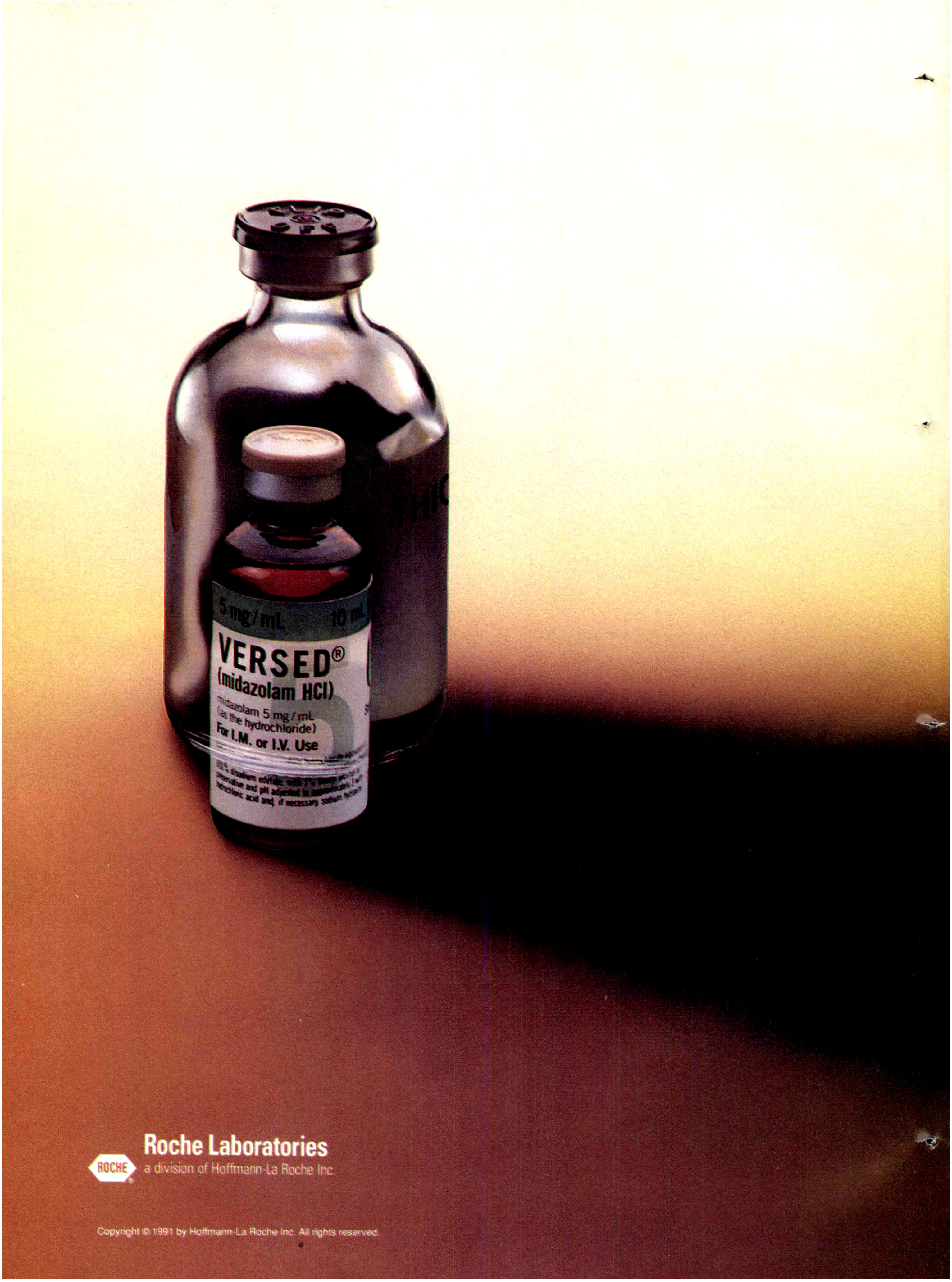
P.O. Box 833, Hackensack, NJ 07602
(800) 338-5803

CHOSEN BY MORE ANESTHESIOLOGISTS THAN ANY OTHER COMPANY IN THE NATION.

Malpractice insurance exclusively
for selected anesthesiologists.

PREFERRED PHYSICIANS MUTUAL
Risk Retention Group

Preferred Physicians Mutual
204 Lucas Place
323 West 8th Street
Kansas City, Missouri 64105
Call Toll-free 800-562-5589



ROCHE®

Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5,6]**
- **Less risk of breakthrough awareness[5,6]**
- **A smooth emergence[5,6]**

Dosing considerations

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE
VERSED®
midazolam HCl/Roche ⒸⅣ
FIRST

Injectable VERSED is available in
1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, *et al.* Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. **4.** Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45–47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology.* 1982;57:279-284. **6.** Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiol Scand.* 1990;34(suppl 92):48-50.

VERSED®
(brand of midazolam HCl/Roche)Ⓥ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

VERSED® (brand of midazolam HCl/Roche)

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particulary narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innover (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

Roche Laboratories
a division of Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

ANESTH ANALG 1991;72:275–81

Cauda Equina Syndrome After Continuous Spinal Anesthesia

Mark L. Rigler, MD, Kenneth Drasner, MD, Tom C. Krejcie, MD, Sharon J. Yelich, MD, Faith T. Scholnick, DO, James DeFontes, MD, and David Bohner, CRNA

RIGLER ML, DRASNER K, KREJCIE TC, YELICH SJ, SCHOLNICK FT, DEFONTES J, BOHNER D. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991;72:275–81.

Four cases of cauda equina syndrome occurring after continuous spinal anesthesia are reported. In all four cases, there was evidence of a focal sensory block and, to achieve adequate analgesia, a dose of local anesthetic was given that was greater than that usually administered with a single-injection technique. We postulate that the combination of maldistribution and a relatively high dose of local anesthetic resulted in neurotoxic injury. Suggestions that may reduce the potential for neurotoxicity are discussed. Use of a lower concentration and a "ceiling" or maximum dose of local anesthetic to establish the block should be considered. If maldistribution of local anesthetic is suspected (as indicated by a focal sensory block), the use of maneuvers to increase the spread of local anesthetic is recommended. If such maneuvers prove unsuccessful, the technique should be abandoned.

Key Words: ANESTHETIC TECHNIQUES, SPINAL, CONTINUOUS. COMPLICATIONS, NEUROLOGIC—cauda equina. ANESTHETICS, LOCAL—lidocaine, tetracaine.

Continuous spinal anesthesia is a relatively old technique that has potential advantages over both single-injection anesthesia and continuous epidural anesthesia. Despite its long history, clear guidelines for the safe administration of local anesthetics via an indwelling subarachnoid catheter remain to be established. We report four cases from three different institutions in which persistent neurologic deficits occurred after a continuous spinal anesthetic.

Case 1

A 68-yr-old man was scheduled for a transurethral resection of the prostate and a right recurrent inguinal hernia repair. His medical history included hypertension, coronary artery disease, and renal calculi. Previous surgery included a right inguinal hernia repair (performed with a field block), a coronary artery bypass graft, and an L3-4 laminectomy. Although he continued to have low back pain after the laminectomy, the pain was nonradicular and he had no neurologic deficit. Medications included metoprolol, dipyridamole, and aspirin; the latter two had been discontinued before the present surgery.

With the patient in a sitting position, a 22-gauge spinal needle was inserted at the L3-4 level, and a 28-gauge catheter (CoSpan, Kendall Healthcare, Mansfield, Mass.) was advanced 3 cm into the subarachnoid space; no paresthesias were elicited during placement. The patient was turned to the supine horizontal position and a total of 150 mg of 5% lidocaine hydrochloride with 7.5% glucose (Astra Pharmaceutical, Westboro, Mass.) was administered in three divided doses over a 15-min period until sensory blockade to a T-8 level was achieved. An additional 25 mg of 5% lidocaine and 0.25 mg of preservative-free morphine (Duramorph, Elkins-Sinn, Cherry Hill, N.J.) were injected through the catheter 1 h later. The catheter was easily removed after the 3-h procedure.

On the following day, the patient was noted to have a left S-1 to S-4 radiculopathy, which showed only minor improvement over the next several days. Computed tomography results were unremarkable. Initial neurologic assessment was that the deficit was secondary to patient positioning during surgery. However, as bowel and bladder dysfunction became apparent, a cauda equina syndrome was diagnosed.

Received from the Departments of Anesthesia, University of California, San Francisco, San Francisco, California; Northwestern University, Chicago, Illinois; Suburban General Hospital, Norristown, Pennsylvania; and Kaiser Permanente, Orange County, California. Accepted for publication December 17, 1990.

Address correspondence to Dr. Drasner, Department of Anesthesia, San Francisco General Hospital, Room 3S-50, 1001 Potrero, San Francisco, CA 94110.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Seven months postoperatively, the patient had to strain to urinate, was unable to have a spontaneous bowel movement, and was experiencing numbness of his penis, left testicle, anus, and left posterior thigh and buttock.

Case 2

A 45-yr-old woman was scheduled for a bilateral bunionectomy and wedge osteotomy. Her medical history included only an uncomplicated vaginal delivery with epidural analgesia and a short regimen of ciprofloxacin for a recent urinary tract infection. With the patient in a right lateral decubitus position, a 22-gauge spinal needle was inserted at the L3-4 interspace and a 28-gauge catheter (CoSpan, Kendall Healthcare) was advanced 1 cm into the subarachnoid space. No paresthesias were elicited with either needle or catheter placement. Fifty milligrams of 5% lidocaine hydrochloride with 7.5% glucose (Astra Pharmaceutical) was administered, followed by an additional 50 mg of lidocaine with an "epinephrine wash" of the syringe, resulting in sensory blockade to T-6 sensory level and motor blockade to L1-2. During the 3.5-h procedure, an additional 200 mg of lidocaine in divided doses was administered through the catheter, primarily to treat tourniquet pain. The catheter was removed without difficulty at the end of the procedure. Four hours postoperatively, perineal numbness persisted and the patient was unable to void. Twelve days later, she still had hypesthesia and hypalgesia bilaterally in the S-3 to S-5 distribution. Anal sphincter tone was diminished and anal reflexes were absent. Lumbosacral spine films and lumbosacral magnetic resonance imaging results were within normal limits. Forty days postoperatively, the patient continued to be unable to void or defecate spontaneously. There is slight recovery of anal wink. She can walk normally.

Case 3

A 56-yr-old man was scheduled for excision of a right saphenous neuroma. His medical history included a 4-yr history of chronic pain along the medial and lateral aspect of the right ankle, which followed a fracture. Radiologic bone scan of the ankle was consistent with reflex sympathetic dystrophy. Several lumbar sympathetic blocks with local anesthetic (paravertebral approach) performed 4 mo before the present surgical procedure produced incomplete pain relief. His previous surgeries included an open reduction and internal fixation of the fractured right ankle, followed by hardware removal and a subsequent arthroscopic examination of the same ankle. All of these surgeries were performed with a spinal anesthetic.

With the patient in a right lateral decubitus position, a 22-gauge spinal needle was placed into the subarachnoid space at the L3-4 interspace on the second attempt, and a 28-gauge catheter (CoSpan, Kendall Healthcare) was advanced 4 cm into the space. The patient experienced a transient paresthesia in the left posterior thigh on advancing the catheter from 1 to 2 cm. A total of 110 mg of 5% lidocaine hydrochloride with 7.5% glucose (Astra Pharmaceutical) was administered in four separate doses over a 20-min period with the patient in a supine horizontal position. The onset of sensory blockade began in the left leg but did not extend to the surgical site (right medial ankle). Consequently, two additional doses of 25 mg were administered more rapidly with the patient in Trendelenburg position, and sensory blockade to the T-10 level was achieved. Surgery then proceeded uneventfully. An additional 30 mg was added during the hour-long procedure, and the catheter was removed without difficulty at the end of surgery. Later that evening, the patient complained of dribbling urine, and the next morning he was unable to empty his bladder. Neurologic examination found impaired sensation to pinprick in the perineal region. Magnetic resonance imaging results were within normal limits. Cystometrogram performed 8 and 35 days postoperatively showed reduced sensation of urgency. Electromyography was inconclusive but consistent with a cauda equina lesion. Ten months postoperatively, the patient still required intermittent urinary catheterization and rarely had a spontaneous bowel movement.

Case 4

A 67-yr-old man was scheduled for a femoral-posterior tibial artery bypass. His medical history included peripheral vascular disease, hypertension, and moderately severe chronic obstructive pulmonary disease; medications included theophylline, metaproterenol, beclomethasone, hydrochlorothiazide-triamterene, aspirin, indomethacin, digoxin, and potassium supplements. Previous operations included a right and a left femoral-popliteal bypass. Both previous surgeries were performed with continuous spinal anesthesia, and the anesthetist was the same as in the present case.

With the patient in a right lateral decubitus position, an 18-gauge Tuohy needle was placed at the L3-4 interspace and a 20-gauge catheter (Perifix, Burron, Bethlehem, Pa.) was inserted 2.5 cm into the subarachnoid space; no paresthesias were elicited during placement. The patient was turned to the supine horizontal position and a total of 20 mg of 1% tetracaine (Winthrop-Breon, New York, N.Y.), diluted with an equal volume of 10% dextrose in water, was injected in three separate doses over a period of 20 min; only a right sacral block developed. Noting that the expiration date of the tetracaine was that month, the anesthetist opened a different ampule (which had 3 yr remaining before expiration) and administered another 8 mg. Surgery proceeded 5 min later. An additional 9 mg of tetracaine was administered over the next 2.5 h. At the end of surgery, 0.25 mg of preservative-free morphine (Duramorph, Elkins-Sinn) was given through the catheter. The patient was moving his legs 3 h later in the recovery room and was monitored overnight in the surgical intensive care unit. The spinal catheter was removed the following morning. After the Foley catheter was removed, the patient could void only small amounts; 2 days postoperatively the Foley catheter was reinserted and 1200 mL of urine was obtained. The patient began to have episodes of fecal incontinence, noticed that he was unable to feel the Foley catheter, and complained of dysesthesias in the perineal area. Neurologic assessment confirmed a sensory deficit to pinprick and vibration in the S-3 to S-5 distribution bilaterally with preservation of position sense. Poor rectal sphincter tone was also noted. Computed tomography was unremarkable. Electromyography showed extensive changes consistent with denervation in all the nerve roots tested; that is, abnormal spontaneous activity, increased polyphasic morphology, and decreased recruitment of motor units in lumbar and sacral nerve roots from L-2 to S-4. Although there was some progression from anesthesia to dysesthesias in the perineal area in the initial 2 wk after surgery, no further recovery took place. Thirty-one months postoperatively, the patient required self-catheterization and was unable to have a bowel movement spontaneously.

Discussion

Serious neurologic complications rarely occur after spinal anesthesia (1–4). When they do, the logical first step is to distinguish whether the deficit is or is not directly related to the anesthetic procedure (5,6). The sacral location and multiple root involvement that occurred in these four cases make it extremely unlikely that patient positioning and/or the surgical procedure were the underlying causes. It is interesting, however, that initial neurologic assessment of the first case attributed the injury to patient positioning; it was only when the extent of anal sphincter and bladder dysfunction were appreciated that connection to the anesthetic procedure was considered.

Delays in diagnosis also occurred in cases 3 and 4 for a different reason: in both, urinary dysfunction was not initially perceived as an unusual postoperative complication. Normal ambulation and lack of complaints about bowel function (the initial presentation was constipation) in these two older men resulted in their complaints being overlooked for 1 and 2 wk, respectively.

In all four cases, a cauda equina syndrome was ultimately diagnosed. This syndrome is characterized by varying degrees of urinary and fecal incontinence, sensory loss in the perineal area, and motor weakness in the legs (3). The potential causes include direct or indirect trauma, ischemia, infection, and neurotoxic reaction. Direct needle-induced trauma to the spinal cord during lumbar puncture rarely has long-lasting neurologic sequelae (7). Such cases are generally associated with paresthesias at the time of lumbar puncture followed by persistent back or leg pain, continuing paresthesias, and/or numbness of the feet or legs, usually localized to one side of the body (7,8). The passage of a catheter into the subarachnoid space may pose an additional risk. In a comparative study of single-dose and continuous spinal anesthesia performed with a ureteral catheter, a higher incidence of paresthesias and blood taps occurred with the continuous technique (9). However, catheters have been passed as far as 35 cm within the subarachnoid space without ill effect (10). In the present cases, catheter placement was not associated with obvious trauma; in only one case was a mild transient paresthesia noted. Intraneural injection, another type of traumatic injury, is usually preceded by paresthesia and persistent pain during injection, neither of which occurred in the present cases (11). Most significantly, the neuropathology occurring in these cases would be difficult to explain by a single direct traumatic event. Trauma to nerve tissue may also result indirectly from an expanding epidural hematoma. The clinical findings and diagnostic studies were not consistent with such an etiology. In all four cases, magnetic resonance imaging and/or computed tomography studies showed no evidence of trauma, hematoma, or spinal cord compression.

Spinal cord ischemia may arise from global hypoperfusion or localized ischemia. However, these patients remained hemodynamically stable, and the neurologic findings in these cases are inconsistent with the specific patterns of injury characteristic of localized ischemia (e.g., the anterior spinal artery syndrome [12]).

Infection is extremely unlikely as a cause, given the absence of associated symptoms and the immediate onset and lack of progression of the neurologic deficits. Neurotoxic reactions, which may be immediate or delayed, can occur when contaminants are present or when the wrong substance is unintentionally injected. In the past, cases of chemical meningitis, arachnoiditis, and cauda equina syndrome have resulted from trace amounts of detergents used to clean needles and syringes and from contamination of local anesthetic ampules with alcohol or phenol used during sterilization (13,14). The routine use of disposable syringes and needles and of high-quality heat-sterilized local anesthetics has virtually eliminated this risk (7).

A direct neurotoxic effect of local anesthetic is a possible cause of the observed deficits. In the past, deficits have occurred after spinal anesthesia as a result of excessive anesthetic concentrations and certain local anesthetic formulations (3). In 1937, Ferguson and Watkins described 14 cases of cauda equina syndrome after the use of "heavy" Durocaine, a mixture of 10% procaine in 15% ethanol, glycerine, and gum acacia or gliadin (15). The cause of the injury was thought to be the vehicle components until it was shown that, in cats, the intrathecal administration of 10% procaine alone could produce similar deficits (16). In general, the authors' description of the neurologic deficits was similar to those that occurred in the present cases.

Whether currently used concentrations of local anesthetics have the potential to produce similar injuries is controversial. Recent reviews of local anesthetic tissue toxicity mention the rarity of nerve damage when local anesthetics are administered at usual clinical concentrations (17–20). In some animal models, the concentrations of various local anesthetics required to produce irreversible conduction blockade or permanent histologic changes exceed clinically administered concentrations of these agents (17,21,22). In rabbits, persistent functional deficits were observed only with the intrathecal injection of 8%, not 4%, lidocaine (23). Similarly, intrathecal injection of commonly used local anesthetic solutions in dogs via indwelling subarachnoid catheters, including 5% lidocaine and 0.5% tetracaine, produced no prolonged deficits or histologic changes (24). A series of studies was published in the 1980s after several reports of permanent neurologic deficits following inadvertent subarachnoid injection of epidural dosages of 2-chloroprocaine (25,26). In an isolated rabbit vagus nerve preparation, 3% chloroprocaine, but not 2% lidocaine or 0.75% bupivacaine, produced conduction defects and histologic damage (27). Initial studies indicated that the neurotoxic effect of chloroprocaine might be the result of its relatively low pH. However, later studies suggested that toxicity was related to a combination of low pH and the presence of sodium bisulfite (28). The overall conclusion of many investigators was that chloroprocaine per se was not neurotoxic (17,18).

In contrast, other animal studies have demonstrated the potential neurotoxicity of clinical concentrations of local anesthetics. In rabbits, lesions of the cauda equina were observed in some animals after the intrathecal injection of 4% lidocaine; however, they were not consistently produced with concentrations less than 16% (23). In in situ rat sciatic nerve experiments, solutions of 3% chloroprocaine, 1% tetracaine, 2% lidocaine, or 0.75% bupivacaine applied exteriorly to the epineurium have produced significant endoneurial edema (29). Electron microscopy of these preparations revealed abnormal mast cells, Schwann cell injury, and axonal dystrophy. Further studies by the same investigators found that histologic evidence of nerve injury correlated well with both anesthetic potency and concentration. For example, 0.5 mL of 10% procaine produced severe nerve injury, whereas 1 mL of 5% procaine did not (30). On the other hand, repeated administration of 0.5% bupivacaine to rat sciatic nerve was not associated with histologic changes, but significantly decreased the amplitude of evoked action potentials (31).

Perhaps less well known is the potential for clinical concentrations of all local anesthetics to produce neurologic sequelae if administered intrathecally in relatively large doses. Permanent neurologic deficits have been produced in sheep by subarachnoid administration of large (epidural) doses of 3% 2-chloroprocaine, 0.75% bupivacaine, and 2% lidocaine (32). Duration of exposure of neural tissue to local anesthetic may be another factor in the development of neurotoxicity. In rats, subarachnoid infusion of 0.5% bupivacaine, 1.5% lidocaine, and 2% 2-chloroprocaine resulted in neurotoxic injury attributable to duration of exposure, not to specific type of local anesthetic used (33). Although it is difficult to compare directly the results from different animal models, local anesthetics do appear capable of inducing long-lasting structural and functional changes in neural tissue when administered at a high enough dose or concentration.

In all four of the present cases, the amounts of local anesthetic administered were greater than those usually given with the single-injection technique. However, dosages of local anesthetic commonly used intraspinally are tailored to achieve an appropriate dermatomal level and duration, not to avoid neurotoxicity. There are several reports of continuous spinal anesthesia in which dosages of local anesthetic greater than those used for single-injection spinal anesthesia have been administered without ill effect (34–36). In Lemmon and Paschal's classic study of 1000 cases, the largest dose given to any patient was 2200 mg of procaine; this led them to conclude that "this would indicate an individual tolerance and points out, too, that the [correct] dose in any given case is *enough*" (34). Similarly, continuous intraspinal administration of 150–550 mg of hyperbaric 5% lidocaine hydrochloride (in dextrose) produced no adverse neurologic outcome; doses of lidocaine as high as 250 mg were used to establish the initial blockade (36). Continuous spinal anesthesia also has been administered for periods as long as 14 days without permanent neurologic sequelae (37). Interestingly, repeated injections of local anesthetic into the subarachnoid space have been associated with tachyphylaxis (38).

Although high doses have been administered without ill effect, local anesthetic toxicity may have been responsible for the three cases of severe urinary retention (one persisted after discharge) described in Apgar's series of 422 cases of continuous spinal anesthesia (39). Although she made no connection between this complication and dosage of local anesthetic, the highest dose administered was 1700 mg of procaine.

There is evidence that suggests that the neurotoxic potential of a local anesthetic might be unmasked if maldistribution occurs and if the drug were restricted to a small volume of cerebrospinal fluid (CSF). In 1946, Nicholson and Eversole reviewed 21,000 tetracaine spinal anesthetics that had been performed at the Lahey Clinic (16). Three cases of cauda equina syndrome were found, two with a continuous spinal technique. In one of these two, the patient received a total of 38 mg of tetracaine, yet the anesthetic level never went above the T-11 dermatome. After surgery, the patient was unable to move her legs. An obstruction at the 11th thoracic segment was diagnosed. Subsequent laminectomy revealed metastatic carcinoma to the cord, dura, and vertebrae. The authors concluded that the spinal anesthetic had precipitated clinical manifestation of the patients' underlying neurologic disease, but they recognized the additional possibility that mechanical blockage from the tumor could have restricted the spread of local anesthetic and thus resulted in a toxic concentration of local anesthetic.

The focal nature of the sensory blockade in all four of the present cases suggests that intrathecal maldistribution of local anesthetic occurred. Several characteristics of catheters, particularly microcatheters, can permit maldistribution. In the supine position, the peak of the lumbar lordosis is generally at the third or fourth lumbar vertebra. If, in the supine horizontal position, the catheter tip is caudal to the peak of this curve, sacral accumulation of local anesthetic may occur, particularly if a hyperbaric solution is administered. Evidence for this may be found in a study by Mörch et al. in which CSF concentrations of lidocaine were measured at 2-, 15-, and 30-min intervals after injection through an intrathecal catheter (36). The concentration of lidocaine in the CSF aspirated from a catheter, the tip of which lay in the sacral area, was almost nine times greater at 15 min than the mean concentration aspirated from other catheters with tips appropriately located in a cephalad position. (The former patient had a "low" block and required general anesthesia.) Unintentional sacral positioning of the tip of an intrathecal catheter may occur more frequently with a small catheter because the straight needle used for placement has less ability to control the catheter's initial direction, and the catheter's small size and flexibility may allow it to be easily deflected downward in the subarachnoid space.

The rate of injection of local anesthetic solution through a catheter may also affect distribution. Because of the higher resistance, the maximum rate of injection through a microcatheter is much lower than that through a larger "epidural" catheter and could contribute to nonuniform distribution of anesthetic (40). That is, the concentration of local anesthetic would not be evenly or rapidly diluted by the surrounding volume of CSF. In addition, the high resistance of the small catheter makes it more likely that a small syringe and, thus, a higher concentration of local anesthetic would be selected, adding to the potential for neurotoxicity.

Of course, nonuniform distribution can occur with single-injection spinal anesthesia; it may well be the most common cause of a "failed spinal." However, when maldistribution results in a "failed spinal," anesthetists will usually either repeat the lumbar puncture or administer a general anesthetic. Unlike the repeated single-injection anesthetic, the presence of an indwelling catheter in a relatively fixed position allows an anesthetist to repeat the same mistake in a rather precise way, i.e., "the same spot on the fence may be painted again and again." Although sufficient

P 24,544.

amounts of local anesthetic may finally extend far enough to produce adequate anesthesia, this may occur only after anesthetic concentrations have reached neurotoxic levels in other areas of the subarachnoid space.

In addition to toxicity from local anesthetic, there are other microenvironmental factors that could have been responsible for or contributed to the nerve damage that occurred. Repeated intrathecal administration of hyperbaric local anesthetic can lower the pH of CSF and increase its baricity and glucose concentration. It is interesting to note, however, that low pH has been postulated to contribute to the development of tachyphylaxis as well as to neurotoxicity (38,41).

We have presented four patients who developed sacral root deficits after continuous spinal anesthesia. All four patients continue to have varying degrees of bladder and bowel atony, as well as perineal sensory deficits, although they are able to ambulate normally. Recognition of the link between anesthetic procedure and neurologic deficit was delayed in three of the four patients.

It appears that the combination of maldistribution and a relatively high dose of local anesthetic exposed neural tissue to a toxic concentration of anesthetic. Thus, if maldistribution occurs, neurotoxicity can result even when local anesthetics are administered in normal clinical concentrations and at total dosages well below an inadvertent subarachnoid injection of an intended epidural dose. In addition, we believe that the use of a microcatheter is more likely to result in maldistribution. However, as the fourth case illustrates, the use of a large catheter does not entirely eliminate this possibility.

The clinical practice of using a spinal catheter to "titrate" the extent and profundity of anesthesia by incremental intrathecal injection of small amounts of local anesthetic may not always be safe. Although further research is needed, the following suggestions might reduce the potential for neurotoxicity: (a) a catheter should be inserted just far enough into the subarachnoid space to confirm and maintain placement; this may decrease the possibility of sacral accumulation of anesthetic; (b) the lowest effective concentration of local anesthetic should be selected; (c) after a test dose, the extent of blockade should be assessed, and if maldistribution of anesthetic is suspected, maneuvers such as changing patient position, altering the lumbosacral curvature, switching to a different baricity of local anesthetic, and/or manipulating catheter position should be used; and (d) if these maneuvers fail to correct the problem, the technique should be abandoned.

We thank Winifred von Ehrenburg for her expert editorial assistance.

References

1. Noble AB, Murray JG. A review of the complications of spinal anaesthesia with experiences in Canadian teaching hospitals from 1959 to 1969. Can Anaesth Soc J 1971;18:5–17.
2. Dripps RD, Vandam LD. Long-term follow-up of patients who received 10,098 spinal anesthetics—failure to discover major neurological sequelae. JAMA 1954;156:1486–91.
3. Kane RE. Neurologic deficits following epidural or spinal anesthesia. Anesth Analg 1981;60:150–61.
4. Phillips OC, Ebner H, Nelson AT, Black MH. Neurologic complications following spinal anesthesia with lidocaine—a prospective review of 10,440 cases. Anesthesiology 1969;30: 284–9.
5. Greene NM. Neurological sequelae of spinal anesthesia. Anesthesiology 1961;22:682–98.
6. Cousins MJ, Bridenbaugh PO. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade in clinical anesthesia and management of pain. Philadelphia: Lippincott, 1988:253–360.
7. Vandam L. Complications of spinal and epidural anesthesia. In: Orkin F, Cooperman L, eds. Complications in anesthesiology. Philadelphia: Lippincott, 1983:75–105.
8. Vandam LD, Dripps RD. Long-term follow-up of patients who received 10,098 spinal anesthetics IV. JAMA 1960;172:1483–7.
9. Dripps RD. A comparison of the malleable needle and catheter technics for continuous spinal anesthesia. NY State J Med 1950;50:1595–9.
10. Saklad M, Dwyer CS, Kronenberg S, Neves E, Sorkin M. Intraspinal segmental anesthesia: a preliminary report. Anesthesiology 1947;8:270–87.
11. Selander D. Paresthesias or no paresthesias. Acta Anaesthesiol Belg 1988;39(Suppl 2):173–4.
12. Ackerman WE, Mushtaque MJ, Knapp RK. Maternal paraparesis after epidural anesthesia and cesarean section. So Med J 1990;83:695–7.
13. Gibbons RB. Chemical meningitis following spinal anesthesia. JAMA 1969;210:900–2.
14. Seigne TD. Aseptic meningitis following spinal anaesthesia. Anaesthesia 1970;25:402–7.
15. Ferguson FR, Watkins KH. Paralysis of the bladder and associated neurologic sequelae of spinal anaesthesia (cauda equina syndrome). Br J Surg 1937;25:735–52.
16. Nicholson MJ, Eversole UH. Neurological complications of spinal anesthesia. JAMA 1946;132:679–85.
17. Strichartz GR, Covino BG. Local anesthetics. In: Miller RD, ed. Anesthesia. New York: Churchhill Livingstone, 1990:437–70.
18. Carpenter RL, Mackey DC. Local anesthetics: In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical anesthesia. New York: Lippincott, 1989:371–403.
19. Steen PA, Michenfelder JD. Neurotoxicity of anesthetics. Anesthesiology 1979;50:437–53.
20. Lampert DH. Complications of spinal anesthesia. Int Anesth Clin 1989;27:51–60.
21. Pizzolato P, Renegar OJ. Histopathologic effects of long exposure to local anesthetics on peripheral nerves. Anesth Analg 1959;38:138–41.
22. Adams HJ, Mastri AR, Eicholzer AW, Kilpatrick G. Morphologic effects of intrathecal etidocaine and tetracaine on the rabbit spinal cord. Anesth Analg 1974;53:904–8.

23. Ready LB, Plumer MH, Haschke RH, Austin E, Sumi SM. Neurotoxicity of intrathecal local anesthetics in rabbits. Anesthesiology 1985;63:364–70.

24. Feldman HS, Covino BG. A chronic model for investigation of experimental spinal anesthesia in the dog. Anesthesiology 1981;54:148–54.

25. Ravindran RS, Bond VK, Tasch MD, Gupta CD, Luerson TG. Prolonged neural blockade following regional anesthesia with 2-chloroprocaine. Anesth Analg 1980;59:447–54.

26. Moore DC, Spierdijk J, van Kleef JD, Coleman RG, Love GF. Chloroprocaine neurotoxicity: four additional cases. Anesth Analg 1982;61:155–9.

27. Barsa J, Batra M, Fink BR, Sumi SM. A comparative in vivo study of local neurotoxicity of lidocaine, bupivacaine, 2-chloroprocaine, and a mixture of 2-chloroprocaine and bupivacaine. Anesth Analg 1982;61:961–7.

28. Wang BC, Hillman DE, Spielholz NI, Turndorf H. Chronic neurological deficits and Nesacaine-CE—an effect of the anesthetic, 2-chloroprocaine, or the antioxidant, sodium bisulfite? Anesth Analg 1984;63:445–7.

29. Myers RR, Kalichman MW, Reisner LS, Powell HC. Neurotoxicity of local anesthetics: altered perineurial permeability, edema, and nerve fiber injury. Anesthesiology 1986;64:29–35.

30. Kalichman MW, Powell HC, Myers RR. Quantitative histologic analysis of local anesthetic-induced injury to rat sciatic nerve. J Pharmacol Exp Ther 1989;250:406–13.

31. Kyttä J, Heinonen E, Rosenberg PH, Wahlstrom T, Gripenberg J, Huopaniemi T. Effects of repeated bupivacaine administration on sciatic nerve and surrounding muscle tissue in rats. Acta Anaesthesiol Scand 1986;30:625–9.

32. Rosen M, Baysinger CL, Shnider SM, et al. Evaluation of neurotoxicity after subarachnoid injection of large volumes of local anesthetic solution. Anesth Analg 1983;62:802–8.

33. Li DF, Bahar M, Cole G, Rosen M. Neurological toxicity of the subarachnoid infusion of bupivacaine, lignocaine or 2-chloroprocaine in the rat. Br J Anaesth 1985;57:424–9.

34. Lemmon WT, Paschal GW. Continuous-serial, fractional, controllable intermittent-spinal anesthesia, with observations on 1000 cases. Surg Gynecol Obstet 1942;74:948–56.

35. Kallos T, Smith TC. Continuous spinal anesthesia with hypobaric tetracaine for hip surgery in lateral decubitus. Anesth Analg 1972;51:766–73.

36. Mörch ET, Rosenberg MK, Truant AT. Lidocaine for spinal anaesthesia. A study of the concentration in the spinal fluid. Acta Anaesthesiol Scand 1957;1:105–15.

37. Ansbro FP, Latten FS, Blundell AE, Sweeney J, Androko JE, Bodell B. Prolonged spinal anesthesia. Anesthesiology 1954;15: 569–71.

38. Greene NM. Physiology of spinal anesthesia. Baltimore: Williams & Wilkins, 1981.

39. Apgar V. Continuous spinal anesthesia. Anesthesiology 1942: 640–3.

40. Hurley RJ, Lampert DH. Continuous spinal anesthesia with a microcatheter technique: preliminary experience. Anesth Analg 1990;70:97–102.

41. Cohen EN, Levine DA, Colliss JE, Gunther RE. The role of pH in the development of tachyphylaxis to local anesthetic agents. Anesthesiology 1968;29:994–1001.

Should You Cancel the Operation When a Child Has an Upper Respiratory Tract Infection?

Marsha M. Cohen, MD, MHSc, FRCPC, and Cal B. Cameron, MD, FRCPC

COHEN MM, CAMERON CB. Should you cancel the operation when a child has an upper respiratory tract infection? Anesth Analg 1991;72:282–8.

Cancelling an operation when a child has an upper respiratory tract infection (URI) is not always feasible or practical. Yet we know very little about the additional risk posed by a URI occurring in a child undergoing anesthesia and surgery. Using a large prospectively collected pediatric anesthesia database, we studied 1283 children with a preoperative URI and 20,876 children without a URI. We found that children with a URI were two to seven times more likely to experience respiratory-related adverse events during the intraoperative, recovery room, and postoperative phases of their operative experience. Although these children also experienced significant disruptions in temperature regulation, they were not at risk for any other deleterious events. The elevation in risk after URI as compared with children without a URI was not explained by differences in age, physical status scores, surgical site, and emergency or elective status. However, if a child had a URI and had endotracheal anesthesia, the risk of a respiratory complication increased 11-fold (95% confidence intervals 6.8, 18.1). We conclude that the administration of general anesthesia to children with a URI is not benign and that these children require more observation/management in all perioperative phases of their surgical procedure.

Key Words: ANESTHESIA, PEDIATRIC—respiratory infections. INFECTIONS, RESPIRATORY—preoperative.

Currently, many anesthesiologists consider postponing an operation when a child is known to have an upper respiratory tract infection (URI) (1). However, this is not always possible, especially when the family has traveled from a rural or remote area or if the case is an emergency. To determine if a URI is deleterious to the outcome of anesthesia and surgery, we used a large pediatric anesthesia database (n = 29,220) to compare morbidity and mortality among children with and without a URI in the perioperative period.

Methods

The Anesthesia Follow-up Program at Winnipeg Children's Hospital has been described previously (2). In brief, from 1982 onward, the pediatric anesthesiologists at the hospital completed a specially designed anesthesia follow-up form for each case. The form contained information regarding age, preoperative coexisting medical conditions, and the American Society of Anesthesiologists' physical status score (3). There was no attempt to quantify the degree of the preexisting illness, only the presence or absence of the condition was noted. The preoperative medical conditions recorded by the anesthesiologist included upper respiratory problems; lower respiratory conditions (asthma or cystic fibrosis); cardiovascular, musculoskeletal, metabolic (diabetes or thyroid disorders), or renal conditions; conditions chronically treated with medication (bronchodilators, anticonvulsants); or "other" conditions (includes congenital, neurologic, and hematologic disorders). Consistent definitions of the variables were used throughout the study period (1982–1987).

During the course of the operation, any intraoperative events requiring action on the part of the anesthesiologist were recorded on the same anesthe-

---

Supported in part by a grant from the Children's Hospital Research Foundation (Winnipeg) and by a National Health Research Development Programs National Health Scholar award to Dr. Cohen.

Presented in part at the International Anesthesia Research Society annual meeting, Honolulu, Hawaii, March 1990.

Received from the Departments of Community Health Sciences and Anesthesia, University of Manitoba, Winnipeg, Canada. Accepted for publication October 31, 1990.

Address correspondence to Dr. Cohen, Clinical Epidemiology Unit (A443), Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, North York, Ontario, Canada M4N 3M5.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

sia record. Selected adverse events that occurred during the immediate recovery period were added to the record by the recovery room nursing staff. Within 72 h of the procedure, an anesthesia follow-up nurse or respiratory therapist reviewed all inpatient anesthesia records for accuracy and completeness, and any events the anesthesiologist may have failed to document were added to the anesthesia follow-up record. The reviewer also examined the patient's hospital chart and recorded any untoward events experienced by the patient recorded by nursing or medical staff. Whenever possible, an interview was carried out with the child or parents to learn of any problems with the anesthetic experience. The results of the interviews and chart reviews were added to the follow-up record. For outpatients, most parents were phoned the day after the procedure to learn of any postoperative complaints. The completed follow-up form was then sent to the attending anesthesiologist for final review before data processing. Because the anesthesiologists' billing card was incorporated into the anesthesia record and follow-up form requiring that both be filled out simultaneously, compliance with the follow-up program was excellent.

To study possible adverse outcomes associated with a URI, we eliminated those children from the database who had preoperative medical conditions other than "upper respiratory." To confirm that only children with URIs remained after these exclusions, from the database (n = 29,220) we identified all cases in which preoperative medical conditions included an upper respiratory airway problem (n = 1724). From these cases, one of us (C.B.C.) reviewed 100 randomly selected hospital charts (that is those marked "upper respiratory problem"). Of the 100 charts, four were unavailable, 53 were marked "upper respiratory problem," and 43 were "upper respiratory problem" plus another medical condition. A further review of the 53 cases of interest to us found that only four did not meet our criteria, two having "stridor" and two "laryngeal web." Thus the number of cases misclassified due to our methodology was extremely small and unlikely to affect the final results.

There were 1283 cases of children having a URI and no other preoperative medical conditions who were the subject of this analysis. There was insufficient information in the database to determine the timing of the URI in relationship to the date of surgery or whether the child was symptomatic. However, it was departmental policy that children who had mucopurulent nasal secretions, an elevated white blood count, or positive chest findings did not proceed to the operating room. Therefore, the children with a URI included in the study had clear nasal secretions and may have been febrile but had a clear chest on examination.

At the hospital, there were six pediatric anesthesiologists each year (nine individuals throughout the study period). The definition of a URI was based on departmental protocols that were discussed at staff meetings. Because of the rapid follow-up of children by the anesthesia reviewer, any deviations from the URI protocol would have been immediately apparent. In addition, using the database, we compared the proportion of URI cases by each individual anesthetist over the study period. The proportion of cases of URI per anesthetist varied from 4% to 8% with no one anesthesiologist having a significantly higher or lower proportion of children diagnosed as having a URI.

As a comparison group, we used the remaining children who did not have any preoperative medical conditions (n = 20,876). We compared the age, physical status scores, and site of operation in children with and without a URI, and we determined the rate of intraoperative, recovery room, and postoperative adverse events between the two groups. The relative risk (and 95% confidence intervals) of having each adverse event was compared in children with a URI and children without a URI (4). Statistical significance was determined if the relative risk was greater than one and the 95% confidence intervals did not include unity.

It may be that children with a URI differed from children without a URI with regard to age, physical status, site of operation, endotracheal intubation, inpatient status, or emergency status—differences that in themselves might be related to differences in perioperative respiratory problems in patients with and without a preoperative URI. To examine this possibility, the authors first defined a new outcome variable—any respiratory events. If patients had at least one finding of a respiratory-related complication in either the operative, recovery, or postoperative period, they were assessed as having "any respiratory event." Only patients whose charts were reviewed by the nurse were included in this analysis (n = 17,036). To determine if having a URI was an independent risk factor for any respiratory event, we performed a multiple logistic regression (5) that controlled simultaneously for all the factors listed above. More details on the statistical analysis are given in the Appendix.

Results

Table 1 shows the ages, physical status scores, and site of operation in the two groups of children.

Table 1. Upper Respiratory Infection by Patient Characteristics

	URI (n = 1,283)		No URI (n = 20,876)	
	n	%	n	%
Age				
Less than 1 mo	18	1.40	93	0.45
1–12 mo	108	8.42	1,455	6.97
1–5 yr	814	63.45	10,195	48.84
6–10 yr	218	16.99	5,386	25.80
11+ yr	125	9.74	3,747	17.95
Physical status score				
I	743	57.91	20,156	96.55
II	435	33.90	665	3.18
III	72	5.61	29	0.14
IV	23	1.79	7	0.03
V	6	0.47	1	0.0
Site of operation				
Eye, ears, nose and throat	737	57.44	10,679	51.15
Other head and neck	200	15.59	2,063	9.88
Intraabdominal	27	2.10	1,021	4.89
Extremities	75	5.85	3,592	17.21
Endoscopy	114	8.89	572	2.74
All other	130	10.13	2,949	14.13

URI, upper respiratory infection.

Children in the URI group were more likely to be in the 1–5-yr age range than the children without a URI. Having a URI made for a marked difference in the physical status score assigned preoperatively to the child (Table 1). Of the children without a URI, 96.6% were assessed as physical status I compared with only 57.9% of children with a URI. Children with a URI were more likely to have been undergoing a procedure involving the head and neck (including eye, ears, nose and throat) than children without a URI.

Table 2 shows the rate of intraoperative, recovery room, and postoperative events in children with and without a URI. In each perioperative time period, children with a URI were at a significantly higher risk (two to sevenfold) for a respiratory-related event ($P \leq 0.05$). For example, children with a URI were 4.53 times more likely to have an intraoperative problem with airway obstruction than children without a URI. Children in the study having a URI were not at risk for any adverse events other than respiratory or temperature regulation and had a lower risk for vomiting in the recovery and postoperative periods.

We next examined the risk of adverse respiratory events in children with a URI by age group. Because of small numbers, children under 1 yr of age were grouped together. Table 3 presents the relative risk of having an adverse outcome in children with a URI as compared to children without a URI by four age groups. There was an elevated risk in children of all ages, and no single age group was at a consistently higher risk than any other age group across the six respiratory-related outcomes.

It is possible that the elevation in risk of respiratory adverse events may be explained by the possibility that children with URIs may be somehow different from children without URIs and that these differences may be responsible for the increased risk. Overall, 6.6% of the 17,036 children whose charts were reviewed had at least one respiratory-related event in the operating room, recovery room, or postoperative period. The results of the multiple logistic regression applied to the independent risk of having URI as compared to not having a URI are shown in Table 4. This table gives the relative odds of having a respiratory complication controlling for all other factors in the table. For example, with the increasing age of a child, there was a decreased risk of having a respiratory complication after controlling for differences in physical status score, inpatient status, year of operation, site of operation, of having a URI, and of having had endotracheal anesthesia.

Children with a URI were more likely to have undergone tracheal intubation than children without a URI (although this was related to their operative procedure rather than to the URI). Therefore, we included an interaction term in the analysis. We found that children who had a URI (but had not undergone intubation) were 8.94 times more likely to have an adverse respiratory event than children without a URI who had not undergone intubation. In contrast, in children who had undergone intubation (but did not have a URI), the risk was 5.21 times greater than in children without a URI who had not undergone intubation. For a small number of children who had undergone both intubation and had a URI (about 5% of the cases), the risk of an adverse respiratory event was extremely high (relative odds = 11.13, 95% confidence intervals = 6.84, 18.10) compared with children without respiratory infections who had not undergone intubation.

Discussion

Three recent studies reported in the literature have looked at adverse respiratory events in children with and without a URI. Tait and Knight (6) carried out a retrospective survey of 3585 patients under 20 yr of age who had undergone various surgical procedures in 1982. Children were considered as having a symptomatic (3.4% of cases) or asymptomatic URI (3.7%)

Table 2. Perioperative Events by Upper Respiratory Infection Status

	URI (n = 1,283)		No URI (n = 20,876)			
	n	%	n	%	Relative risk (95% CI)	
Intraoperative events						
None	1,119	87.21	19,278	92.35	0.94	(0.89, 1.00)
Vomiting	12	0.94	131	0.63	1.49	(0.83, 2.67)
Arrhythmia	83	6.47	1,081	5.18	1.25	(1.00, 1.56)
Hypotension	3	0.23	26	0.12	1.88	(0.60, 5.83)
Temperature regulation	2	0.16	10	0.05	3.25	(0.80, 13.21)
Cardiac arrest	0		5	0.02	—	
Airway obstruction	44	3.43	158	0.76	4.53	(3.25, 6.31)^a
Other respiratory	35	2.73	157	0.75	3.64	(2.52, 5.22)^a
Drug complication	2	0.16	49	0.23	0.66	(0.18, 2.48)
Surgical	3	0.23	70	0.34	0.70	(0.23, 2.09)
Death	0		1		—	
Recovery room events						
None	1,075	83.79	18,290	87.61	0.96	(0.90, 1.02)
Laryngospasm	28	2.18	358	1.71	1.27	(0.87, 1.86)
Vomiting	60	4.68	1,308	6.27	0.75	(0.58, 0.97)^a
Cardiovascular	0		38	0.18	—	
Temperature	12	0.94	131	0.63	1.49	(0.83, 2.67)
Airway obstruction	89	6.94	628	3.01	2.31	(1.85, 2.88)^a
Other respiratory	26	2.03	111	0.53	3.83	(2.49, 5.82)^a
Drug-related	1	0.08	34	0.16	0.50	(0.08, 2.77)
Surgical	14	1.09	265	1.27	0.86	(0.51, 1.46)
Postoperative events^b						
Nausea and vomiting	193	19.67	4,175	26.00	0.76	(0.65, 0.87)^a
Sore throat	11	1.12	195	1.21	0.93	(0.51, 1.68)
Headache	8	0.82	181	1.13	0.73	(0.36, 1.45)
Croup	37	3.77	107	0.67	5.66	(3.90, 8.21)^a
Other respiratory	60	6.12	135	0.84	7.29	(5.37, 9.85)^a
Temperature	33	3.36	251	1.56	2.15	(1.50, 3.09)^a
Cardiovascular	3	0.31	29	0.18	1.69	(0.55, 5.23)
Surgical	22	2.24	284	1.77	1.26	(0.82, 1.95)
Other	14	1.43	259	1.61	0.89	(0.52, 1.50)
Death	0		1	0.01	—	

URI, upper respiratory infection.
[a] $P \leq 0.05$ for URI compared to no-URI group.
[b] Rates per 100 charts reviewed. n = 981 for URI-only group, n = 16,055 for no-URI group.

Table 3. Relative Risk of Respiratory Adverse Events for Children With Upper Respiratory Infection Versus No Upper Respiratory Infection by Age Group

	Relative risk			
	<1 yr	1–5 yr	6–10 yr	11+ yr
OR airway obstruction	5.9^a	2.9^a	6.2^{a,b}	7.5^{a,b}
OR other respiratory	1.4	3.6^a	6.2^{a,b}	4.5^{a,b}
RR airway obstruction	9.7^{a,b}	2.0^a	1.1	2.0
RR other respiratory	0.8	4.2^a	2.5^b	5.0^{a,b}
Postoperative croup	27.6^{a,b}	4.0^a	1.1	15.0^{a,b}
Postoperative other respiratory	2.7^a	7.7^a	13.1^{a,b}	5.7^{a,b}

URI, upper respiratory infection; OR, operating room; RR, recovery room.
[a] $P < 0.05$ for URI compared to no-URI group.
[b] Confidence intervals very wide due to small number of children in each category.

based on information from chart reviews. Overall, 1.65% of the children had at least one respiratory complication in the operating room, including laryngospasm, bronchospasm, stridor, and breath holding. The rate of intraoperative respiratory events was 5.31% in asymptomatic children, 1.61% in children with no URI, and 1.64% in children with symptomatic URI. No age breakdowns were included in the

Table 4. Factors Predicting an Adverse Respiratory Event: Logistic Regression Results

Factor	Reference	Relative odds	95% Confidence limits
Age[a]		0.92	0.90, 0.93
Physical status II–V	Physical status I	1.32	1.03, 1.69
Inpatient	Outpatient	1.32	1.14, 1.53
Year of operation:			
1984–1985	1982–1983	1.10	0.93, 1.29
1986–1987	1982–1983	1.14	0.97, 1.35
Head and neck surgery[b]	Other surgical sites	1.27	1.09, 1.48
Elective	Emergency	1.70	1.27, 2.28
URI	No URI, not intubated	8.94	6.04, 13.22
No URI, intubated	No URI, not intubated	5.21	4.21, 6.46
URI and intubated	No URI, not intubated	11.13	6.84, 18.10

URI, upper respiratory infection.

[a] Age was entered into the model as a continuous variable for patients 2 mo of age and older.

[b] Includes eye, ears, nose and throat, and "other head and neck" operations.

study, and the authors found no relationship between physical status scores, intubation status, type of anesthetic, or site of operation and the risk of respiratory complications in children with a URI.

Our rate of intraoperative respiratory adverse outcomes was approximately twice that reported by Tait and Knight (6). Because they ensured that documentation of respiratory complications was well-established in their hospital, it is unlikely that charting would account for all the differences in outcome frequency. However, the magnitude of the increased risk in their study was about threefold, a finding that is similar to ours. One factor examined by Tait and Knight (6) was the potential effect of different anesthetic drugs, a factor that we did not include in our analysis. However, in our hospital, virtually all children received similar medications (2), so we could not examine the contribution of anesthetic drugs to the risk of respiratory problems.

We were also not able to distinguish between symptomatic and asymptomatic cases in our study as did Tait and Knight (6). Nor could we estimate differences in virulence of endemic viruses in the areas in which the two studies were carried out. In addition, there may be differences in patient populations (our hospital serves a high proportion of North American Indian children), and this makes further comparisons between our study and that of Tait and Knight difficult.

Desoto et al. (7) reported on 50 children aged 1–4 yr undergoing otolaryngologic surgery, half of whom had URIs. Noninvasive measurement of oxygen saturation was initiated immediately on arrival in the postanesthesia recovery room. Five patients who had URIs had oxygen saturations below 95% while breathing room air in the recovery room ($P < 0.03$) but without sequelae. The authors conclude that children of this age group are at increased risk for transient postoperative hypoxemia.

A preliminary report by Betts et al. (8) examined the risk of oxygen desaturation (as measured noninvasively), laryngospasm, and bronchospasm in children with and without URIs during the operative and recovery room periods ($n = 158$ children). In their study, desaturation was defined as an oxygen saturation of 90% or less for 2.5 min. The authors found no differences in the frequency of laryngospasm or desaturation in children with an active URI, in those with a recent URI, and in a control group. However, the number of children in the study was probably too small to be able to detect a difference. If the rate of recovery room respiratory events is the same as in our study (that is 3.4%), one would only expect to find five patients among the 158 in the study who would experience an adverse event.

Thus our large study of over 17,000 patients found that children with a URI were four- to sevenfold more likely to have an adverse respiratory event than children without this problem, and this elevated risk was not explained by the children's age, physical status score, site of operation, and emergency status. We were not able to ascertain whether the children truly had a viral illness as opposed to an allergic condition. Noninvasive measurement of oxygen saturation was not available during the first 3 yr of the study and was not included in the database. The other studies mentioned above found either no differences or very low rates of adverse outcomes (6,7). The differences between this study and those reported above probably relate to the large number of children included in our study and to the extension of the follow-up into the recovery room and early postoperative periods.

One additional factor that increased the perioperative risk of respiratory problems was tracheal intubation. The studies mentioned above found no relationship between intubation and postoperative respiratory problems (5,6). However, in our study we examined separate age groups rather than grouping neonates, infants, and 5-yr-old children together. The basis for our doing so was that edema secondary to intubation results in a greater reduction in the cross-sectional area of the trachea of an infant than in an older child. Indeed, the high relative risk of infants developing postoperative croup supports the premise that children with a URI who have undergone intubation are at significant risk of developing a major adverse respiratory event. This supports the "arbitrary" discharge time of 4 h suggested in the literature for children undergoing day surgical procedures (9).

The administration of anesthesia to a child with a URI has always been a controversial issue (10). Concerns about patient safety have resulted in recommendations involving cancellation of elective procedures for periods of 2–6 wk. However, because children, especially those under 2 yr of age, develop URIs 5–10 times per year (11,12), the potential safe time period for the administration of a general anesthetic is very small. Bearing this fact in mind, we conclude the following:

1. There is a need for hospitals to develop discharge criteria for recovery room and day surgery pediatric patients who have a URI before surgery.
2. For children with asymptomatic or mild URI, we recommend the postponement of elective procedures for children under 1 yr of age. For children over 1 and less than 5 yr, the risk/benefit ratio of the surgical procedure must be considered on an individual basis because these children are still at risk for respiratory complications whether or not they had a preoperative respiratory illness. We found children over 5 yr old to have lower rates of respiratory complications (with the risk of respiratory complications decreasing with age). Therefore, older children with URIs may be at less risk because of anatomically larger airways.
3. Although not a part of this study, we recommend that children with significant preoperative symptoms of URI should have their surgery postponed. If children with relatively minor URIs are at high risk for respiratory problems, it is likely that children with greater preoperative problems would be at an even higher risk.

The authors thank the members of the Department of Anesthesia, Children's Hospital, Winnipeg Manitoba, R. B. Tate and L. MacWilliam for assistance with the statistical analysis, and Dr. P. G. Duncan for his comments on earlier drafts.

Appendix: Statistical Methods

It is possible that factors other than having a URI may be related to an increased risk of respiratory complications and thereby explain the elevated risk found when each factor is examined individually. To assess the importance and independent role of an individual factor (such as URI) we used a multiple logistic regression that controls simultaneously for all factors in the model. To choose the best model to predict the risk of having "any respiratory complication," a number of preliminary steps were taken. First, we tested each factor in Table 4 for an association with the outcome variable (any respiratory complication) by using a χ^2 test. We found that various categorizations of the factors (including continuous, categorical, and dichotomous) had little effect on the results of the analysis. The final choice of categorization was as follows. For age, infants less than 1 mo old were excluded because of small numbers and much higher rates of adverse outcome. All other children were used in the analysis, and the variable "age" was entered as a continuous variable, that is, actual age. Variables such as inpatient status, preoperative URI status, and tracheal intubation were entered as dichotomous (yes, no) variables. For site of operation the two sites "eye, ears, nose and throat" and "other head and neck" were combined, and the variable used was "head and neck surgery"—yes or no. Variables such as year of surgery and physical status scores were entered as "dummy" variables to aid interpretation.

Two interactions were found in the preliminary analysis. First, children with URIs were more likely to have higher physical status scores than children without URIs. We entered an interaction term in the multiple logistic regression model for physical status and URI. However, this interaction term was not statistically significant and therefore was not retained in the final model. A second interaction term was used because children with URIs were more likely to have tracheal intubation than children without URIs. This interaction term was statistically significant and was therefore retained in the final model. The reference category was therefore "no URI, not intubated."

A few cases were excluded due to missing values, leaving 16,684 cases used in the final logistic regression model.

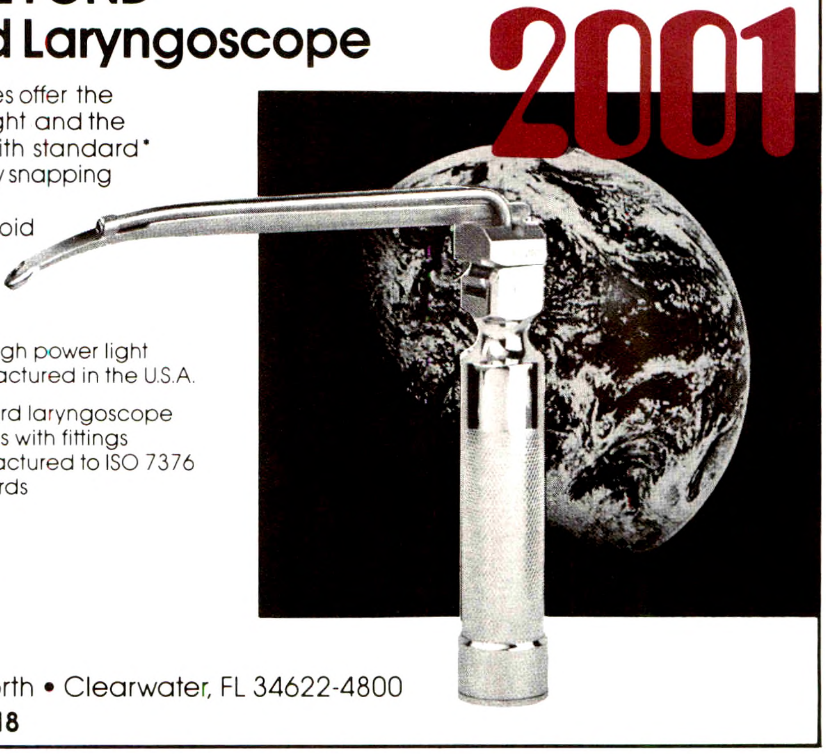
References

1. Gregory G. Outpatient anesthesia. In: Gregory G, ed. Pediatric anesthesia. Volume 1. New York: Churchill-Livingstone, 1983: 406.
2. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anesth Analg 1990;70:160–7.
3. Saklad M. Grading of patients for surgical procedures. Anesthesiology 1941;2:281–5.
4. Kahn HA, Sempos CT. Statistical methods in epidemiology. Oxford: Oxford University Press, 1989.
5. Walker SH, Duncan DB. Estimation of the probability of an event as a function of several independent variables. Biometrika 1967;54:167–79.
6. Tait AR, Knight PR. Intraoperative respiratory complications in patients with upper respiratory tract infections. Can J Anaesth 1987;34:300–3.

7. Desoto H, Patel RI, Soliman IE, Hannallah RS. Changes in oxygen saturation following general anesthesia in children with upper respiratory signs and symptoms undergoing otolaryngological procedures. Anesthesiology 1988;68:276–9.
8. Betts EK, Miller BE, Jorgenson JJ, et al. URI and perioperative desaturation in children. Anesthesia Patient Safety Foundation Newsletter, June 1989:19.
9. Gregory G. Outpatient anesthesia. In: Greogry G, ed. Pediatric anesthesia. Volume 1. New York: Churchill-Livingstone, 1983: 535.
10. McGill WA, Coveler LA, Epstein BS. Subacute upper respiratory infection in small children. Anesth Analg 1979;58:331–3.
11. Monto AS, Ullman BM. Acute respiratory illness in an American community: the Tecumseh study. JAMA 1974;227:164–9.
12. Denny FW. The replete pediatrician and the etiology of lower respiratory tract infections. Pediatr Res 1969;3:464–70.

MERCURY
M E D I C A L

GO LIGHT YEARS BEYOND
With Your Standard Laryngoscope



The 2001 Fiberlight laryngoscope blades offer the advantages of high power halogen light and the convenience of interchangeability with standard* handles. Go light years ahead by simply snapping the Mercury 2001 Fiberlight to your standard* conventional handle, and avoid the cost of completely replacing your current laryngoscope system.

Features

- No electric wires in blade
- No electric switches
- No special handle required
- Non-glare matte finish
- Focused light
- Easy lamp replacement
- Chrome-plated brass construction
- Cool high power light
- Manufactured in the U.S.A.

*Standard laryngoscope handles with fittings manufactured to ISO 7376 standards

MERCURY
M E D I C A L
11300A - 49th Street North • Clearwater, FL 34622-4800
TOLL FREE 1-800-237-6418

Anesthesiology Review Seminar

Sponsored by Creighton University School of Medicine and Professional Seminars, Inc
April 15-22, 1991 San Diego

Unlimited Mock Oral Practice Sessions

Creighton University and Professional Seminars, Inc. present an intensive review seminar intended for practicing physicians needing to fulfill their **CME requirements** and candidates preparing to take their **oral or wirtten board exam.** Emphasizing fundamental principles and clinical practice, lectures will reflect the leading edge of current techniques and research.

The faculty selected for the Anesthesiology Review Seminar are among the best teachers on the lecture circuit today. Involved in spearheading new research and discovery, they provide participants with **fresh perspective and enthusiasm** as well as a current knowledge base.

Daily mock oral sessions give individual attention to each participant. Practice examiners will help polish your presentation by teaching you thought organization and delivery. **Special sessions** are scheduled to teach you the *do's* and *don'ts* of taking the oral exam and to explain how the actual exam is scored.

Home study material is available upon request to enable candidates to focus on areas needing attention at the course.

Attendance at this seminar **will be kept low** to enable faculty and staff to attend to the individual needs of each participant. Only the **first 100** registrations will be accepted.

For a complete list of **topics, faculty or references**, call Professional Seminars, Inc. at 1-800-445-4564 or wirte to P.O. Box 498, Clinton, IN 47842. To register for this course, call Creighton University, CME Division at 1-800-548-2633.

*"Your **limited registration** was definitely a plus. It gave me the opportunity to work individually with the faculty and **made me more relaxed** about the upcoming exam."*

*"Participating in the mock orals gave me the **practice and confidence I needed.** After your course, I felt prepared..."*

*"Attending your course **just before** my exam was the best thing I could have done to prepare for my actual exam. I passed on my **first try**. I will recommend it to my associates."*

Creighton University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Creighton University School of Medicine designates this continuing medical education activity for **60 hours in Category 1** of the Physicians Recognition Award of the American Medical Association. One credit hour may be claimed for each hour of participation by physicians.

Name____________________
Address____________________
City/St/Zip____________________
Phone____________________
Social Security #____________________
Visa/Mastercard____________________ exp.________

$675 - San Diego April 15-20
$120/day-extra mock orals Apr. 21,22
$450 - repeating or residents
Pay to: Professional Seminars, Inc.
Mail to: Creighton University
Division of CME
California at 24th Street
Omaha, NE 68178

Extensive *and* Intensive

THE 16TH ANNUAL

Specialty Review in Anesthesiology

May 11 – 17, 1991

• Chicago •

Even more extensive (a full 7 days) and intensive (61 AMA Category 1 credit hours) than last year. Covers the entire clinical spectrum of anesthesiology; also reviews fundamental principles. Ideal for candidates preparing for certification or for experienced clinicians who want a thorough review.

*"Absolutely superb format, presentations, and speakers."**

*"Very good – helped me catch up with current trends."**

Course Coordinator: Alon P. Winnie, M.D., Professor of Anesthesiology, University of Illinois College of Medicine at Chicago.

For more information, call toll-free anytime

1-800-621-4651

Presented by

THE COOK COUNTY GRADUATE SCHOOL OF MEDICINE

The CME Leader

Or write to us at
707 South Wood Street
Chicago, Illinois 60612

The Cook County Graduate School of Medicine is not affiliated with the County of Cook or any of its agencies, including Cook County Hospital.

*Comments of previous registrants.

Pan-Pacific Surgical Association

21st Biennial Congress
January 26-30, 1992

Hilton Hawaiian Village, Honolulu, Hawaii
Separate sessions for
nine surgical specialties
and Anesthesiology
Post-Congress Meeting
Grand Hyatt Wailea, Maui
January 31 and February 1, 1992

For information contact:

The Pan-Pacific Surgical Association office
733 Bishop Street, #1910
Honolulu, Hawaii 96813

Phone (808) 523-8978 FAX (808) 599-3991

ANESTHESIA

Opportunity to join a busy pediatric anesthesia practice located at a children's hospital that is the major referral center for a tri-state area. All surgical procedures are performed including pediatric and neonatal open-hearts. Preferred candidates should be board eligible/board certified with pediatric-anesthesia experience. Competitive financial arrangements.

Mail C.V. to:

P A A

Pediatric Anaesthesia Associates, P.S.C.

Attn: S. Manecke
2000 Warrington Way, Suite 250
Louisville, KY 40222-6409

The University of Massachusetts Medical Center is currently recruiting for a:

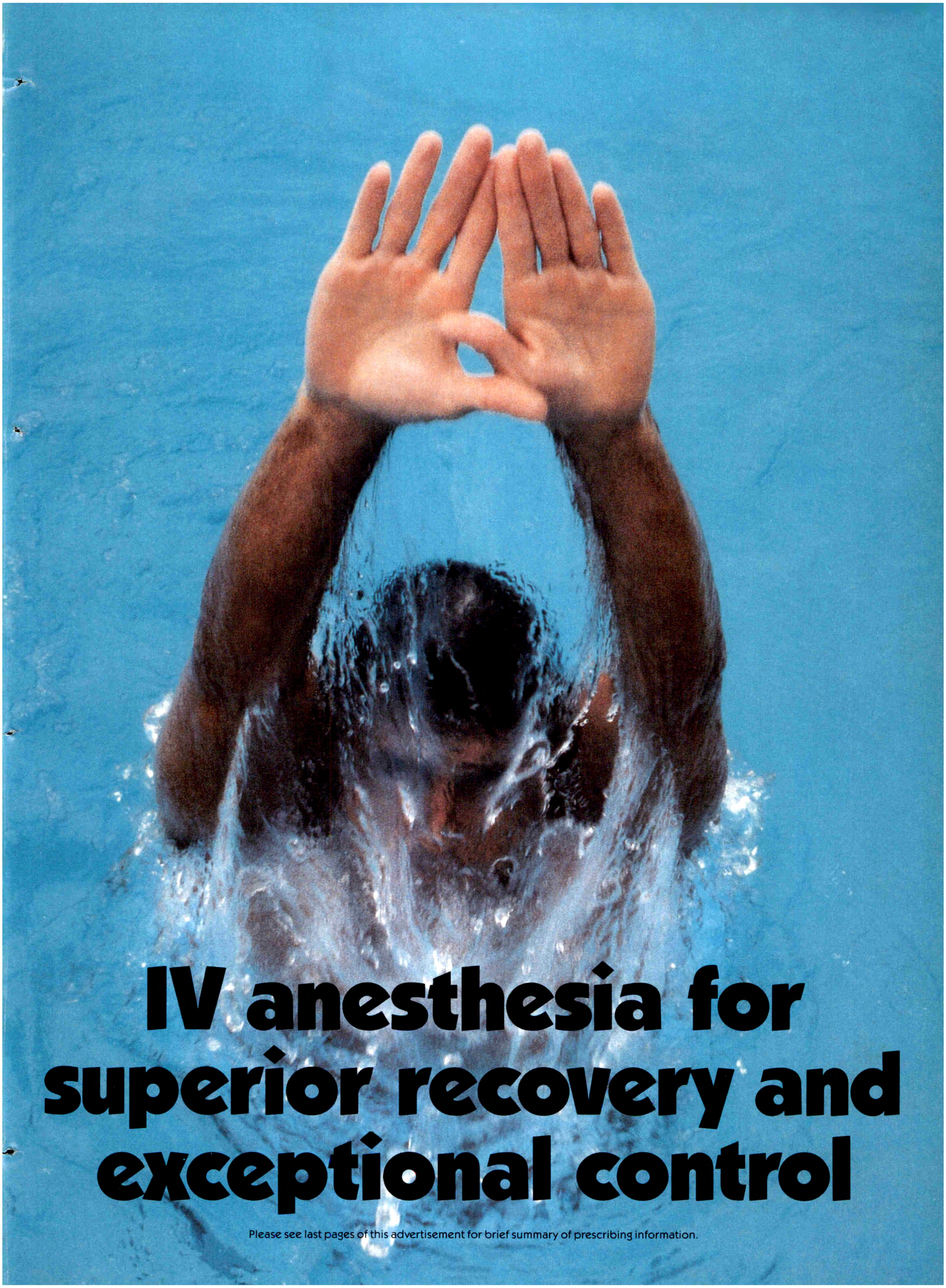
Director, Pain Control Services

Department of Anesthesiology, University of Massachusetts Medical Center, is seeking a board certified anesthesiologist for Director, Pain Control Services. Prerequisites include experience in acute and chronic pain medicine and academic experience sufficient to warrant initial appointment as Associate Professor. Responsibilities include directorship of a multidisciplinary outpatient pain control center with more than 6,500 patient visits per year and responsibility for overseeing an acute pain consulting service which performs approximately 1,500 new consultations per year.

Send C.V. to: Gary Welch, MD, PhD, JD, Chairman, Department of Anesthesiology, University of Massachusetts Medical Center, Worcester, MA 01655.

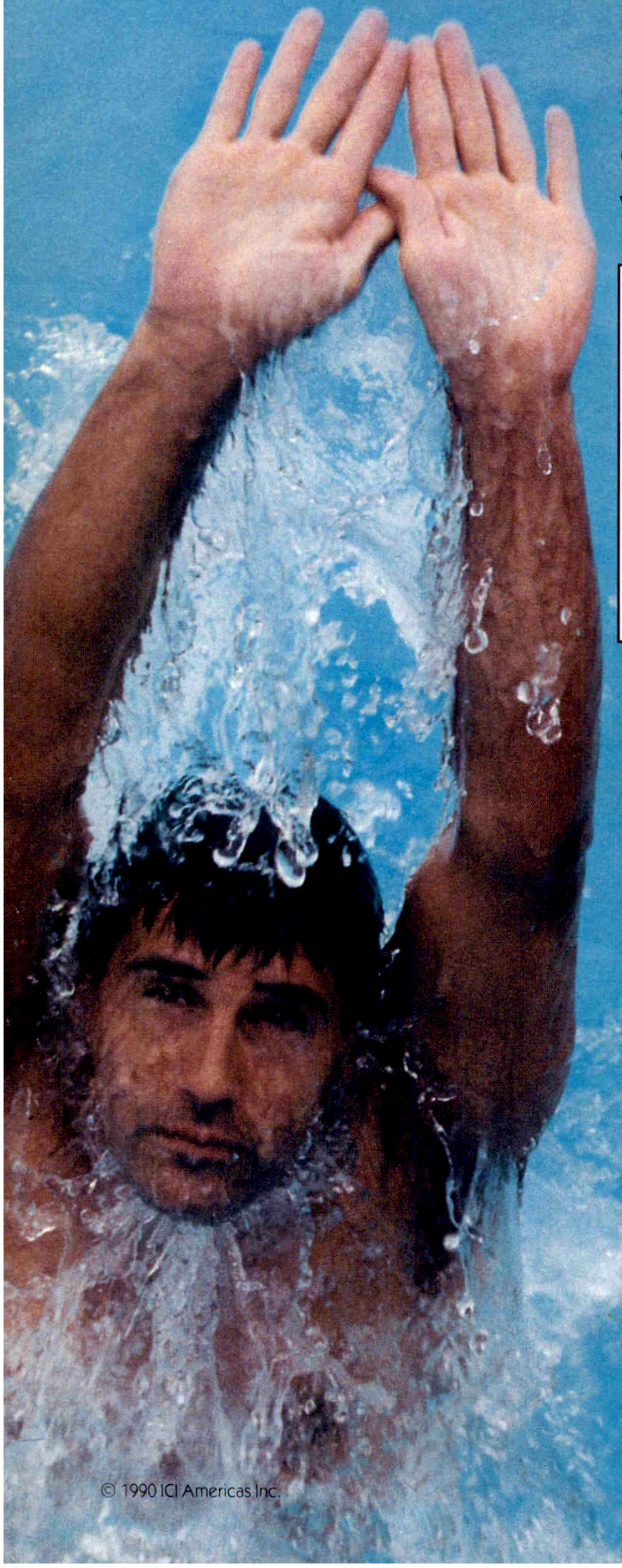
The University of Massachusetts is an Equal Opportunity/Affirmative Action Employer.

UMASS MEDICAL CENTER


IV anesthesia for superior recovery and exceptional control

Please see last pages of this advertisement for brief summary of prescribing information.

Superior exceptional



Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

© 1990 ICI Americas Inc.

recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

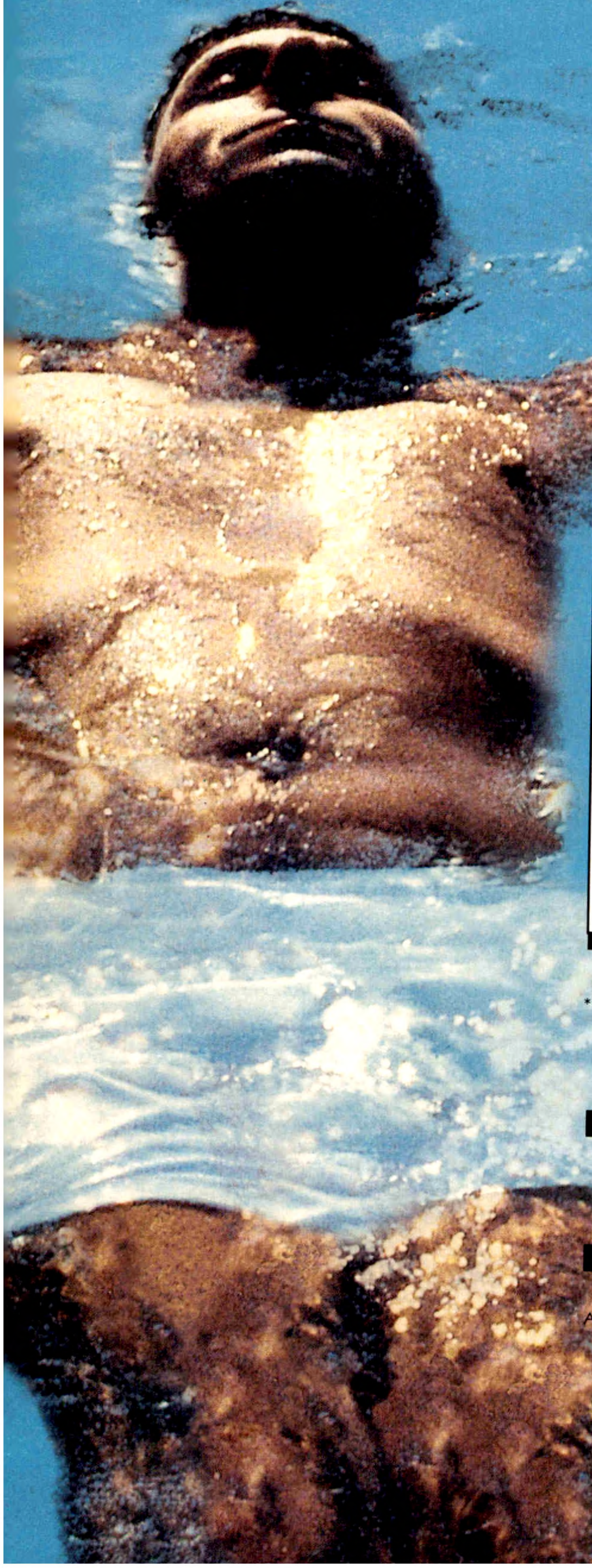
As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

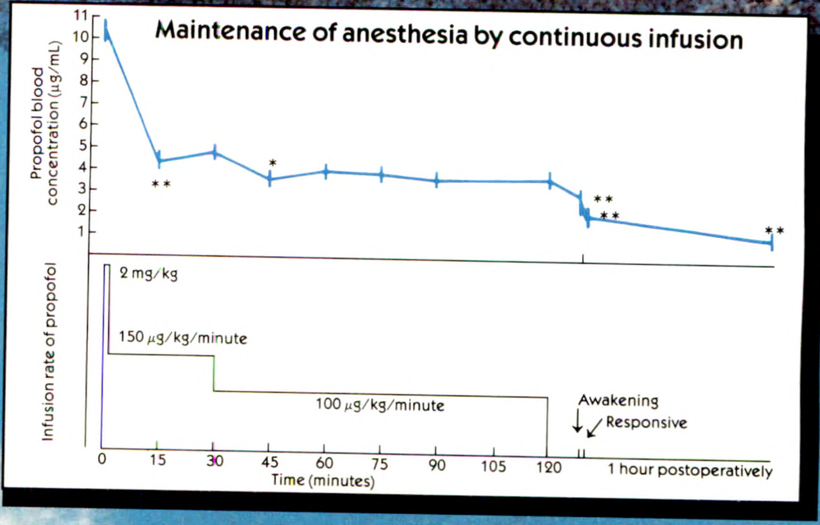
DIPRIVAN®
INJECTION
propofol

Superior exceptional



Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration


Maintenance of anesthesia by continuous infusion

—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)
After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Since the vehicle (soybean oil in water emulsion) is capable of supporting rapid growth of microorganisms, strict aseptic technique must always be maintained while handling DIPRIVAN Injection. (See WARNINGS and DOSAGE AND ADMINISTRATION sections in the brief summary of prescribing information at the end of this advertisement.)

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

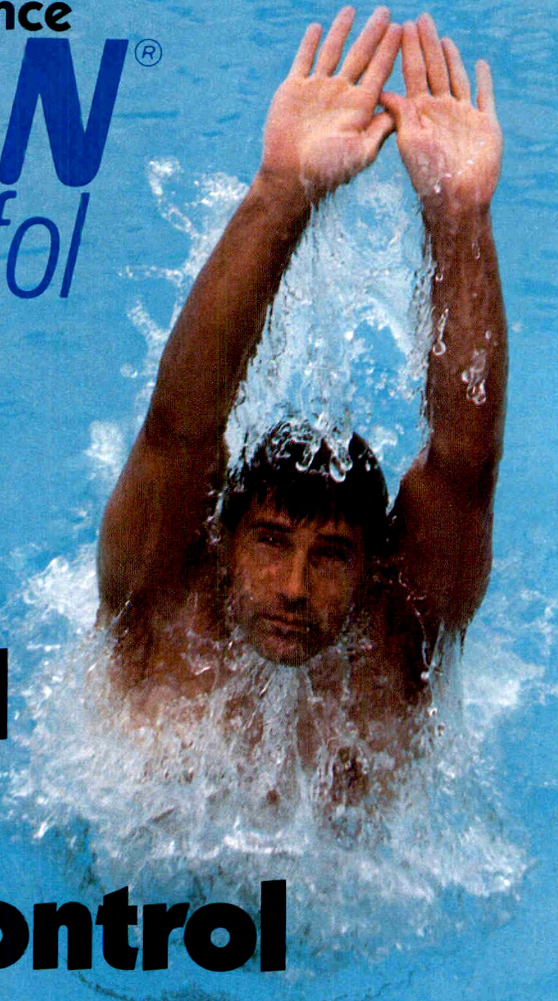
For induction and maintenance

DIPRIVAN®
INJECTION
propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol



Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia,

Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

Incidence of unmarked events is 1%-3%. *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized*.)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine*.

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized*.)

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia*. **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus*. **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia*. **Special Senses:** Ear Pain, *Nystagmus*. **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

- 5% Dextrose Injection, USP
- Lactated Ringers Injection, USP
- Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

Made in Sweden
Manufactured for:
STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

The Osler Institute

Anesthesiology Boards Review Course

§April 15-20, 1991 – San Diego

July 6-11, 1991 – Chicago §Sept. 30-Oct. 5, 1991 – Tampa

Now offering §60 hours of mock oral exams limited to 90 participants

Co-sponsored by the University of Washington

OBJECTIVES

After this program attendees should:

- Have improved basic and clinical anesthesia knowledge
- Be better organized for further study of anesthesiology
- Be prepared to take written and oral exams

METHODS

- HOME STUDY MATERIALS consisting of a syllabus and assignments with questions and answers
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

PHYSIOLOGY

Respiratory Physiology
Cardiovascular Physiology
Neurophysiology
Hepatic Physiology
Renal Physiology
Acid-Base and Blood Gas
Endocrine Physiology
Thermoregulation

PHARMACOLOGY

Pharmacokinetics
Inhalation Anesthetics
Intravenous Anesthetics
Muscle Relaxants
Autonomic Drugs
Central Nervous Drugs
Cardiac & Diuretic Drugs
Interactions & Genetics

PHYSICAL SCIENCES

Applied Anatomy
Physics and Gas Laws
Anesthesia Machines
Instrumentation
Monitors and Ventilators
Breathing Systems
Defibrillators and Pacers

FUNDAMENTALS

Preop. Evaluation & Prep.
Patient Monitoring
Airway Management
Fluid and Blood Therapy
Cardiopulmonary Disease
Hepatic & Renal Disease
Metabolic Disease
Recovery Room

REGIONAL ANESTHESIA

Local Anesthetics
Autonomic Blocks
Spinal and Epidural Blocks
Caudal Blocks
Upper Extremity Blocks
Lower Extremity Blocks
Chronic Pain Management

SPECIALTY AREAS

Obstetric Anesthesia
Pediatric Anesthesia
Cardiac Anesthesia
Thoracic Anesthesia
Neuroanesthesia
Ophthalmic & E.N.T.
Geriatric and Outpatients
Critical Care

FACULTY

Ezzat Abouleish, M.D.
U. of TX Med. Sch., Houston

Steven Barker, Ph.D., M.D.
Univ. of California, Irvine

Jonathan Benumof, M.D.
Univ. of California, San Diego

T. A. Bowdle, M.D., Ph.D.
University of Washington

Burton Briggs, M.D.
Loma Linda University

Hernando DeSoto, M.D.
Riverside Hosp., Jacksonville

John Drummond, M.D.
Univ. of California, San Diego

Richard Engel, M.D.
Palomar Hosp., Escondido, CA

Christopher Gallagher, M.D.
Anes. Services, San Diego

Richard Hanberry, M.D.
Lawrenceville, Georgia

Carl Hess, M.D.
Univ. of California, Irvine

Niels Jensen, M.D.
University of Iowa

David Lubarsky, M.D.
Duke University

Terence Murphy, M.D.
University of Washington

Danae Powers, M.D.
Emory University

Michael Ritter, M.D.
St. Louis University

David Rothenberg, M.D.
Rush Medical School

Amira Safwat, M.D.
University of California, Davis

Mark Scheller, M.D.
Univ. of California, San Diego

Daniel Siker, M.D.
Medical College of Wisconsin

Ngoc-Hai Truong, M.D.
FHP Hosp., Fountain Valley, CA

John Viljoen, M.D.
Univ. of Southern California

K.C. Wong, M.D.
University of Utah

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name ______________________________

Address______________________________

City/State/Zip__________________________

Phone ______________________________

Mail today to:

1094 Dawn Lane, Dept. 103
P.O. Box 2218
Terre Haute, IN 47802

For: ☐ April 15-20, 1991 – San Diego
☐ July 6-11, 1991 – Chicago
☐ Sept. 30-Oct. 5, 1991 – Tampa
☐ Check enclosed for $________
☐ Please send more information

*"Accommodations were comfortable...."**

LOCATION: The April course will be at the San Diego Princess Resort in Mission Bay, 1404 West Vacation Road, San Diego, California.

*"I feel [the course] helped me pass...."**

PROGRAM: This course is designed to prepare you for your board exams. Upon registration we will send you our home study material. At the course, one-on-one mock oral exams are held concurrent with most lectures. Each participant is assured a mock oral exam and observation of all non-private exams. You may reserve mock oral sessions at any course and optional extra days of mock oral exams — April 21-23. Past participants recommend repeating the course for half price just before your exams.

*"...the most education for the money."**

FEES AND CATEGORY 1 C.M.E.:

• 6 day lectures and mock orals:	$660
Residents and Fellows fee:	$440
Repeating course within 3 years:	$330
• Mock oral observation only (6 day):	$400
Per day mock oral observation:	$ 70
• Single examiner mock oral exam:	$ 70
• Dual examiner mock oral exam:	$140
• Surcharge for private exam:	$ 30
• Surcharge for videotaped exam:	$ 10
• Previous course syllabus:	$ 60

- Attendees not in course hotel add $20/day.
- A deposit of $50 will reserve your position.
- Most home study materials will be mailed after half of the registration fee is received.
- Subject to a $50 fee, refunds will be made up until the seminar begins.
- The University of Washington School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians. The University of Washington School of Medicine designates this Continuing Medical Education activity for up to **90 credit hours** in **Category 1** of the Physician's Recognition Award of the American Medical Association.

*"...home study material was extremely helpful."**

INFORMATION:

Joseph H. Selliken, Jr., M.D.
The Osler Institute
1094 Dawn Lane, P.O. Box 2218
Terre Haute, IN 47802
(800) 356-7537 or (812) 299-5658

* *Comments by past Osler participants*

§ Plus optional extra days Apr. 21-23 & Oct. 6-8.

Shield against surgical stress

SUFENTA®
(sufentanil citrate) Injection CII

For longer more stressful procedures

As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

References: 1. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. 2. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. 3. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. 4. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.

Predictable control of stress responses from induction through recovery

***REDUCES** stress response to intubation and surgical stimulation* [1,2]

***PROVIDES** intraoperative hemodynamic stability*

***CONTROL** of the stress response is associated with less postoperative morbidity* [3,4]

***MAINTAINS** postoperative analgesia with faster recovery of respiratory drive* [5]

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.
DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 μg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.
INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.
CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 μg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 μg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 μg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 μg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.
Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.
Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.
ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:
Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement
DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

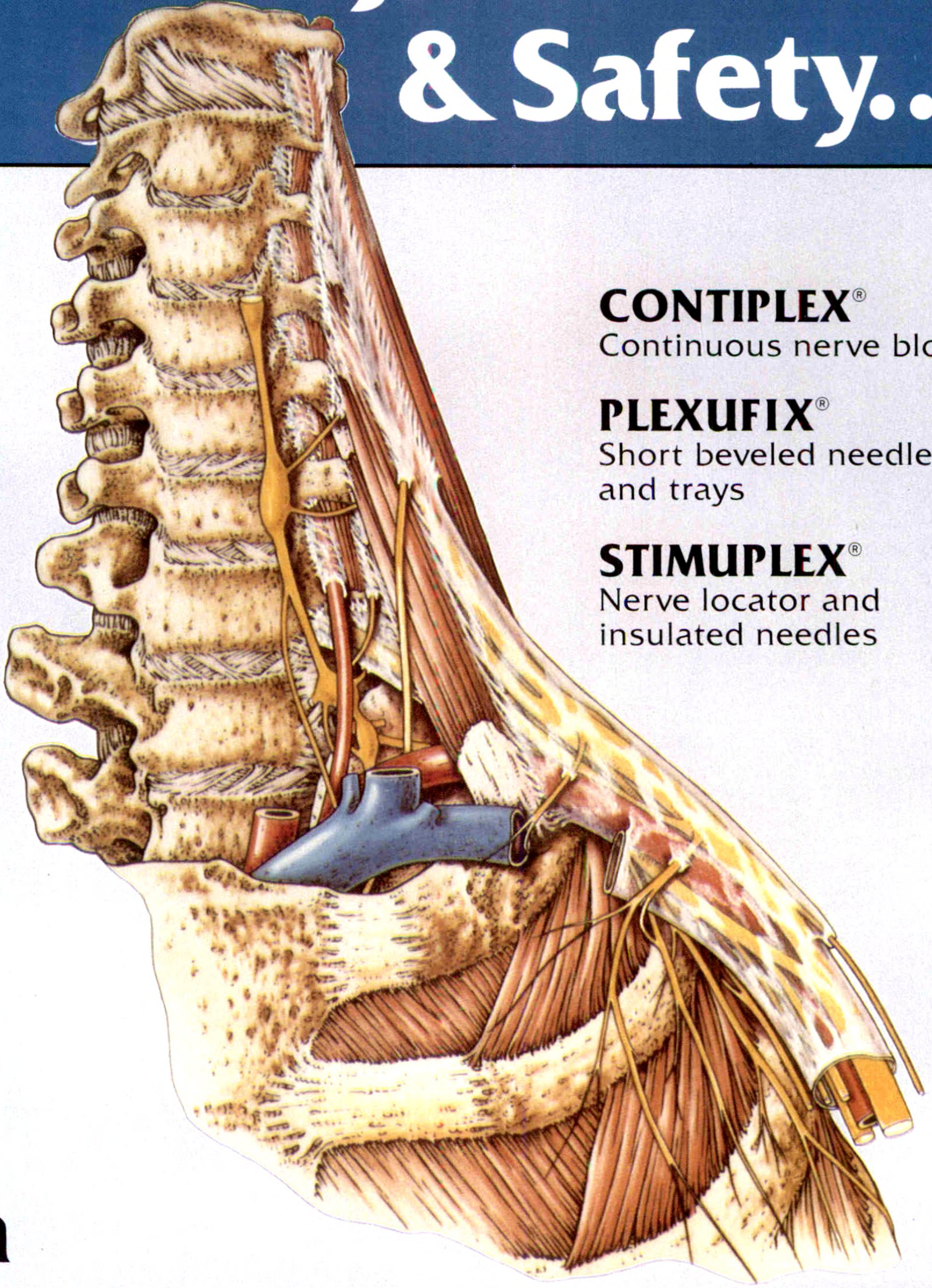
world leader in anesthesia research

JANSSEN
PHARMACEUTICA

Piscataway, NJ 08854

March 1986, March 1987
U.S Patent No. 3,998,834
7618505-M

© Janssen Pharmaceutica Inc. 1989 JPI-SU-025A-R



Accuracy, Precision & Safety...

CONTIPLEX®
Continuous nerve block

PLEXUFIX®
Short beveled needles
and trays

STIMUPLEX®
Nerve locator and
insulated needles

in
NERVE BLOCK ANESTHESIA

BURRON MEDICAL INC.
824 Twelfth Avenue
Bethlehem, PA 18018
800-523-9695 / 215-691-5400
B. Braun of America Company

B.BRAUN

Influence of Desflurane on Regional Distribution of Coronary Blood Flow in a Chronically Instrumented Canine Model of Multivessel Coronary Artery Obstruction

J. Craig Hartman, BS, Paul S. Pagel, MD, John P. Kampine, MD, PhD,
William T. Schmeling, MD, PhD, and David C. Warltier, MD, PhD

HARTMAN JC, PAGEL PS, KAMPINE JP, SCHMELING WT, WARLTIER DC. Influence of desflurane on regional distribution of coronary blood flow in a chronically instrumented canine model of multivessel coronary artery obstruction. Anesth Analg 1991;72:289–99.

The influence of desflurane on myocardial perfusion measured by a microsphere technique during a total occlusion of the left anterior descending coronary artery and concomitant moderate or severe stenosis of the left circumflex coronary artery was evaluated in chronically instrumented dogs. Hemodynamics, regional contractile function, and myocardial blood flow were measured during the conscious state and after anesthesia with desflurane (8.2%–9.2% and 12.5%–12.7%) with and without control of arterial pressure. Total left anterior descending occlusion produced in combination with a left circumflex coronary artery stenosis significantly ($P < 0.05$) increased heart rate and left ventricular end diastolic pressure in the absence of desflurane anesthesia. Desflurane, administered only in the presence of left anterior descending occlusion and left circumflex stenosis, significantly ($P < 0.05$) decreased mean arterial pressure, left ventricular systolic pressure, and left ventricular positive dP/dt_{50} without change in heart rate. Blood flow to the subendocardium of normal myocardium was reduced during the high concentration of desflurane ($P < 0.05$), but perfusion of the subepicardium and midmyocardium was maintained at conscious levels. When the left circumflex stenosis was of moderate severity, only blood flow to the subendocardium distal to the stenosis was reduced by desflurane ($P < 0.05$). In the presence of a severe stenosis, perfusion was decreased in the subepicardium, midmyocardium, and subendocardium of the stenotic zone ($P < 0.05$). During the reduction in arterial pressure produced by desflurane, collateral blood flow in the left anterior descending region was reduced in dogs with either a moderate or severe left circumflex stenosis ($P < 0.05$). When arterial pressure and heart rate conditions observed in the postocclusion conscious state were restored during the high concentration of desflurane, myocardial blood flow in all regions returned to those levels present in the conscious state ($P < 0.05$). Ratios of flow between occluded and normal zones were decreased when hypotension produced by desflurane was uncontrolled, but when arterial pressure and heart rate were adjusted to conscious postocclusion levels using partial thoracic aorta occlusion and atrial pacing, the ratio remained at conscious control levels regardless of the degree of left circumflex stenosis severity ($P < 0.05$). Results of this investigation indicate that desflurane does not redistribute blood flow away from collateral-dependent myocardium to other regions via a "coronary steal" mechanism in a chronically instrumented canine model of multivessel coronary artery disease.

Key Words: ANESTHETICS, VOLATILE—desflurane. ARTERIES, CORONARY—steal. HEART, CORONARY ARTERY DISEASE—coronary steal.

The influence of volatile anesthetics on myocardial blood flow in patients with coronary artery disease has not been well defined. The actions of isoflurane and halothane have been previously characterized in clinical and experimental studies of coronary artery disease (1–6). The new volatile anesthetic desflurane may possess coronary vasodilator activity similar to isoflurane. Such actions have been suggested with isoflurane to produce "coronary steal," a decrease in perfusion of ischemic myocardium occurring during an increase in blood flow to normal zones (3,5,7). Although isoflurane relaxes coronary arterial rings in vitro (8,9) and reduces coronary vascular resistance in vivo (10), this vasodilator activity may not be sufficient to redistribute myocardial blood flow away from

---

Supported in part by U.S. Public Health Service grant HL 36144, VA Medical Research Funds, and Anesthesiology Research Training Grant GM 08377.

Received from the Departments of Anesthesiology, Pharmacology, and Medicine, Medical College of Wisconsin, Milwaukee; and the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication November 6, 1990.

Address correspondence to Dr. Warltier, Department of Anesthesiology, Medical College of Wisconsin, 8701 West Watertown Plank Road, Milwaukee, WI 53226.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

ischemic zones. Isoflurane administered as the sole anesthetic agent to a chronically instrumented canine model of multivessel coronary artery disease did not produce coronary steal in a recent investigation from this laboratory (11). In contrast, adenosine markedly decreased coronary collateral blood flow (11).

Although several studies have described some of the cardiovascular actions of desflurane, none to date have evaluated the influence of this new agent on myocardial perfusion (12–18). The present investigation was designed to characterize the action of desflurane on regional myocardial blood flow in a chronically instrumented canine model of multivessel coronary artery disease. The continuous development of a slowly progressive left circumflex coronary artery constriction was monitored by daily assessment of resting flow velocity and coronary reserve. When the left circumflex stenosis was moderate or severe, the left anterior descending coronary artery was totally occluded to stimulate "coronary steal-prone anatomy" in the conscious state. Desflurane was then administered to determine the influence of this anesthetic on regional myocardial perfusion.

Methods and Materials

Surgical Preparation

All experimental procedures and protocols utilized in this investigation were reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. All conformed to the *Guiding Principles in the Care and Use of Animals* of the American Physiological Society and were in accordance with the *Guide for the Care and Use of Laboratory Animals* [DHEW (DHHS) Publication No. (NIH) 85-23, rev. 1985].

Conditioned mongrel dogs of either sex weighing between 22 and 32 kg fasted overnight. Anesthesia was induced with sodium thiamylal (10 mg/kg IV). After intubation with a cuffed endotracheal tube, anesthesia was maintained with halothane (1.0%–1.5%) in 100% oxygen (1 L/min) during mechanically controlled ventilation. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space and the lungs were gently retracted. Heparin-filled catheters were implanted in the thoracic aorta and the right atrial appendage for measurement of arterial pressure and for drug administration. A catheter was positioned in the left atrial appendage and secured by a purse-string suture. This catheter was used for measurement of left atrial pressure, administration of radioactive microspheres for determination of regional myocardial perfusion, and injection of adenosine for daily assessment of coronary vascular reserve. The heart was suspended in a pericardial cradle, and 1.5–2.0-cm sections of the proximal left anterior descending and left circumflex coronary arteries were isolated. Doppler ultrasonic flow transducers (20 MHz) were placed on each vessel for measurement of phasic and mean coronary blood flow velocity. Distal to the flow transducer, a balloon-cuff vascular occluder (In Vivo Metric Systems, Healdsburg, Calif.) was secured around the left anterior descending coronary artery to permit acute coronary artery occlusion. An Ameroid constrictor was fitted around the left circumflex coronary artery distal to the flow probe to produce a slowly progressive vascular stenosis. No arterial branches were present between flow transducer and vascular occluder or Ameroid constrictor.

A precalibrated, miniature micromanometer (Konigsberg Instruments, Pasadena, Calif., model P7) was inserted into the left ventricular chamber through an incision in the apex and was tightly secured for recording of left ventricular pressure and the rate of rise of left ventricular pressure at 50 mm Hg (dP/dt_{50}). A left ventricular catheter was implanted adjacent to the transducer for subsequent intraarterial infusions of adenosine. The left ventricular micromanometer was cross-calibrated against pressures measured via the left ventricular fluid-filled catheter (Statham, Oxnard, Calif., model P50). Electrodes were sutured to the right atrial appendage for cardiac pacing. Pairs of miniature ultrasonic length transducers were implanted in the subendocardium of the left anterior descending and left circumflex perfusion territories. All catheters and electrical leads were secured, tunneled subcutaneously, and exteriorized between the scapulae through several small incisions. The chest wall was closed in layers and the pneumothorax evacuated by a chest tube. Each dog was fitted with a jacket (Alice King Chatham, Los Angeles, Calif.) to prevent damage to the instruments and catheters, which were housed in an aluminum box within the jacket pocket. After surgery, each dog was allowed to recover for at least 2 days before daily hemodynamic monitoring and was treated with procaine penicillin G (400,000 U IM) and dihydrostreptomycin (560 mg IM). For several days before surgery and during the postoperative recovery period, all dogs were trained to stand quietly in a sling to ensure a stable baseline hemodynamic state.

Regional Contractile Function

Regional contractile function (segment shortening) was measured in the perfusion territories of the left anterior descending and left circumflex coronary arteries by pairs of cylindrical ultrasonic crystals. All signals were continuously monitored via ultrasonic amplifiers (Crystal Biotech, Holliston, Mass.). Using left ventricular dP/dt, end-diastolic segment length (EDL) was determined immediately before the onset of left ventricular isovolumetric contraction. End systolic length (ESL) was determined at the time of maximum negative dP/dt. The lengths were normalized according to the method of Theroux et al. (19). Percent systolic shortening (%SS) was calculated by use of the following equation: %SS = [(EDL − ESL)/EDL] × 100.

Regional Myocardial Blood Flow

Carbonized plastic microspheres (New England Nuclear, Boston, Mass.; 15 ± 2 μm diameter) labeled with ^{141}Ce, ^{103}Ru, ^{51}Cr, or ^{95}Nb were used to measure regional myocardial perfusion (20). Immediately before injection, the sphere suspension was ultrasonicated (E/MC Corporation, model 450) for 15 min and subsequently agitated in a vortex mixer (Cole-Parmer, model 4722) for 5 min. The microsphere injection consisted of approximately 2–3 × 10^6 spheres injected into the left atrial chamber as a bolus over 10 s and flushed in with 10 mL of warm (37°C) sterile saline. A few seconds before the microsphere injection, a timed collection of reference arterial flow was started (precalibrated Harvard infusion/withdrawal pump, model 1941) from the thoracic aortic catheter and maintained at a constant rate of 7 mL/min for 3 min.

At the conclusion of each experiment, transmural tissue samples were selected for mapping of myocardial blood flow. The samples were selected from three zones of the left ventricle: (a) normal region (myocardium proximal to both the hydraulic occluder and Ameroid constrictor); (b) stenotic region (distal to the left circumflex stenosis produced by the Ameroid constrictor); and (c) occluded region (distal to the left anterior descending occlusion produced by inflation of the vascular cuff). Two colored dyes (Monastral Blue B Suspension; India ink) were injected simultaneously into the coronary circulation immediately distal to the hydraulic occluder and Ameroid constrictor at a pressure of 100 mm Hg to identify precisely the occluded and stenotic zones, respectively. Normal myocardium remained unstained. Tissue samples were subdivided into subepicardial, midmyocardial, and subendocardial layers of approximately equal thickness. Samples were weighed and placed in scintillation vials, and the activity of each isotope was determined. Tissue blood flow (Q_m; mL·min^{-1}·g^{-1}) was calculated from the following equation: $Q_m = Q_r \times C_m/C_r$, where Q_r = rate of withdrawal of the reference blood flow sample (mL/min), C_r = activity (cpm) of the reference blood flow sample, and C_m = activity (cpm/g) of the myocardial tissue sample.

Experimental Protocols

Beginning on the second postoperative day, dogs were monitored daily for hemodynamic changes during slowly progressive stenosis of the left circumflex coronary artery. Each animal was brought to the laboratory and placed in a sling. After a short period of adjustment to these conditions (30 min), resting blood flow velocity was recorded in both the left anterior descending and left circumflex coronary arteries. Subsequently, the vascular reserve of myocardium supplied by each vessel was evaluated by administration of adenosine (100 μg) via the left atrial catheter. Reserve in each region was quantified as the percent increase in diastolic coronary blood flow velocity above the resting value elicited on injection of adenosine. When the left circumflex hyperemic response to adenosine was reduced to at least 50% of that observed on the second postoperative day, a stenosis of moderate severity was considered to be present. Dogs that demonstrated a further reduction in the hyperemic response to adenosine and a decrease in resting left circumflex coronary blood flow velocity were considered to have a severe stenosis. When either a moderate or severe left circumflex stenosis developed, the left anterior descending coronary artery was totally occluded by inflation of the hydraulic cuff. The subsequent model of multivessel coronary artery disease was utilized to evaluate the actions of desflurane on systemic hemodynamics, regional myocardial blood flow, and segmental contractile function. All dogs were given procainamide hydrochloride (300 mg IV) and lidocaine hydrochloride (60 mg IV) before cuff inflation to suppress potential ventricular arrhythmias after left anterior descending coronary artery occlusion.

Before experimentation, all dogs fasted overnight. Fluid replacement was accomplished with 0.9% normal saline (approximately 500 mL), and fluid maintenance was continued at 3 mL·kg^{-1}·h^{-1} for the duration of each experiment. During a stable hemodynamic state 30 min after left anterior descending coronary occlusion, radioactive microspheres were injected and control hemodynamic data were recorded. Anesthesia was induced by inhalation of desflurane (15%–20%, 1 MAC = 7.2% [21]) and oxygen. After tracheal intubation, anesthesia was continued with desflurane in oxygen (100–250 mL/

min) and room air (2 L/min) during positive pressure ventilation utilizing a semiclosed anesthesia circuit. Tidal volume was set at 15 mL/kg, and respiratory rate was adjusted to maintain arterial $\mathrm{P}_{\mathrm{CO}_2}$ within the conscious range (30–35 mm Hg). The oxygen-air mixture was adjusted to maintain arterial $\mathrm{P}_{\mathrm{O}_2}$ near conscious levels. In each experiment, the inspired concentration (range 6%–12%) of desflurane was adjusted to produce a reduction in diastolic arterial pressure of approximately 25–30 mm Hg. End-tidal gas tensions and anesthetic concentrations were continuously monitored with an infrared gas analyzer (Datex Capnomac, Helsinki, Finland).

After a 30-min equilibration period to provide a hemodynamic steady state during the first concentration of desflurane, a second set of radioactive microspheres was administered and arterial blood gas tensions were measured. The inspired concentration of desflurane was then changed (range 11%–15%) to produce a 35–40 mm Hg decrease in diastolic arterial pressure below conscious levels. Equilibration at the new anesthetic level was allowed for an additional 30 min before injection of a third set of microspheres. Arterial blood pressure during the high concentration of desflurane was then adjusted to those levels present in the conscious state by inflation of a balloon catheter. The right femoral artery was exposed with a small incision, and the vessel catheterized with a Fogarty occlusion catheter (8/22F, Baxter Corp., Deerfield, Ill.). The catheter tip was advanced to the descending thoracic aorta and the balloon inflated to elevate blood pressure to levels present in the conscious state. During this procedure, heart rate was often reduced by activation of intact autonomic reflexes to levels below those in the control state. Thus, when required during balloon inflation, heart rate was returned to control levels by atrial pacing with an electronic stimulator (Grass SD9 Stimulator, Quincy, Mass.). A final set of radioactive microspheres was injected during the high inspired concentration of desflurane with arterial pressure and heart rate adjusted to control levels. This protocol was completed in both dogs with moderate and severe left circumflex coronary artery stenoses. Dogs were killed with an overdose of sodium pentobarbital at the conclusion of each experiment. The heart was removed, washed with saline, and fixed for 24–48 h in a 10% formaldehyde solution before obtaining specimens for myocardial blood flow analysis.

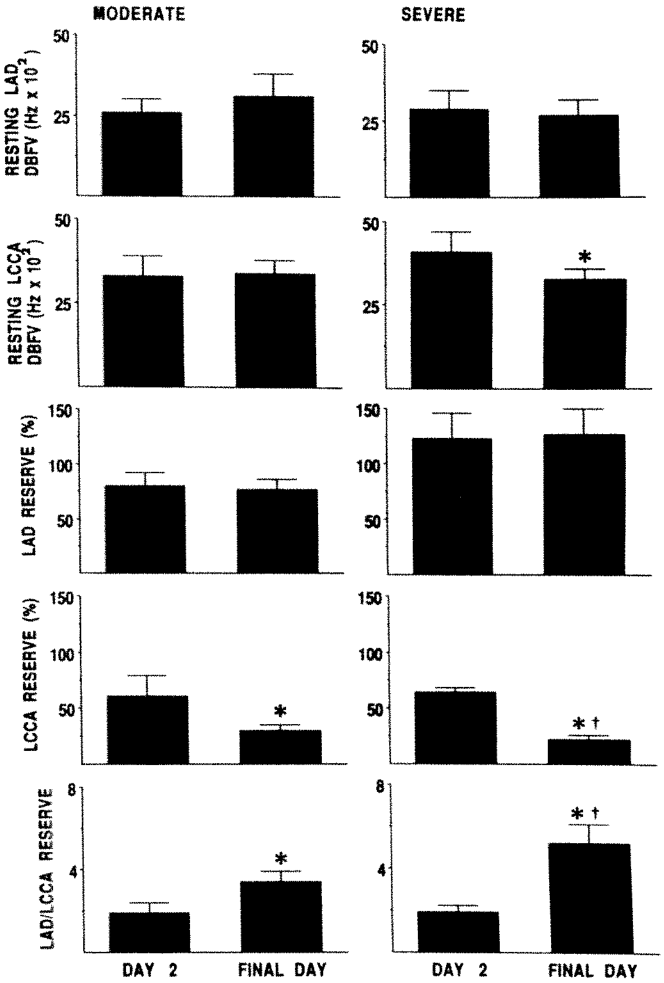


Figure 1. Effects of a moderate (n = 6) or severe (n = 6) left circumflex (LCCA) stenosis on coronary hemodynamics. Postoperative day 2 and the final day of progressive stenosis development are compared. The top two pairs of histograms demonstrate the effects of stenosis on resting diastolic blood flow velocity (DBFV). The bottom three pairs of histograms depict the percent increase in DBFV above resting (LAD or LCCA Reserve [%]) after adenosine and the ratio of those responses (LAD/LCCA Reserve), respectively. LAD, left anterior descending coronary artery. Values are mean ± SEM. *Significant difference from day 2 ($P < 0.05$). †Significant ($P < 0.05$) difference from the final day, moderate stenosis group.

Statistical Analysis

Nineteen dogs were used in the present investigation to provide 12 successful experiments. Three dogs died of intractable ventricular fibrillation, and two dogs died of cardiogenic shock after combined left anterior descending coronary artery occlusion and left circumflex stenosis. Two dogs were excluded from the study because of failure of instrumentation.

Coronary blood flow velocity data collected during development of the left circumflex stenosis were analyzed with paired and unpaired t-tests (22). Hemodynamic, myocardial blood flow, and contractile function data were analyzed with repeated measures one-way and three-way analysis of variance. One-way analysis of variance was used to compare all

Table 1. Hemodynamic Effects of Desflurane in Dogs With a Moderate Left Circumflex Coronary Artery Stenosis

	Before occlusion	After occlusion	Desflurane (8.2%)	Desflurane (12.7%)	Desflurane (BP/HR) (12.7%)
Heart rate (beats/min)	98 ± 10[a]	126 ± 7	134 ± 10	121 ± 9	119 ± 9
Mean arterial pressure (mm Hg)	92 ± 2[a]	106 ± 5	73 ± 3[a]	61 ± 2[a]	103 ± 4
Left ventricular systolic pressure (mm Hg)	125 ± 3	133 ± 3	101 ± 3[a]	87 ± 4[a]	121 ± 5[a]
Left ventricular end-diastolic pressure (mm Hg)	7 ± 1[a]	13 ± 1	18 ± 2[a]	21 ± 3[a]	29 ± 3[a]
$+dP/dt_{50}$ (mm Hg/s)	1930 ± 170	1960 ± 80	1530 ± 140[a]	1190 ± 150[a]	1200 ± 190[a]
LCCA diastolic blood flow velocity (Hz × 10^2)	35 ± 5	40 ± 5	38 ± 7	34 ± 6	37 ± 6
LCCA mean blood flow velocity (Hz × 10^2)	24 ± 4	30 ± 5	30 ± 6	26 ± 4	26 ± 5
LCCA segment shortening (%)	15.8 ± 3.6	15.9 ± 3.3	15.6 ± 3.9	14.4 ± 3.7	9.3 ± 3.1[a]
LAD segment shortening (%)	16.8 ± 2.7[a]	−0.4 ± 1.2	−0.6 ± 0.5	−0.6 ± 0.5	0.2 ± 0.9
Arterial pH	—	7.42 ± 0.01	7.36 ± 0.02	7.39 ± 0.01	—
Arterial P_{CO_2}	—	30 ± 1	30 ± 2	31 ± 3	—
Arterial P_{O_2}	—	83 ± 3	100 ± 7[a]	108 ± 6[a]	—

LCCA, left circumflex coronary artery; BP/HR, blood pressure and heart rate adjusted to "After occlusion" levels via partial aortic constriction and atrial pacing; LAD, left anterior descending coronary artery.

All values are expressed as mean ± SEM ($n = 6$).

Data in the "Before occlusion" and "After occlusion" groups were obtained in the awake state.

[a] Significantly different from "After occlusion" levels ($P < 0.05$).

means with the postocclusion control mean within one of the two treatments, and three-way analysis of variance was used to compare treatments with each other. When overall significance was found with analysis of variance, treatment means were compared by Duncan's multiple range test and considered significant when $P < 0.05$. All data are expressed as mean ± SEM.

Results

Progression of Stenosis Development

All dogs were observed daily until Ameroid constriction of the left circumflex coronary artery reached a moderate (9 ± 2 postoperative days) or severe (12 ± 3 postoperative days) degree of stenosis. Left atrial injections of adenosine, administered daily to ascertain the degree of attenuation in coronary reserve during left circumflex stenosis, produced minimal changes in heart rate and arterial pressure. Sequential changes in coronary hemodynamics in both experimental groups are summarized in Figure 1. Resting left anterior descending coronary blood flow velocity remained unchanged in all dogs during left circumflex stenosis development. By the final day of monitoring left circumflex stenosis development, dogs with a moderate degree of stenosis had no change in resting left circumflex blood flow velocity whereas dogs with severe stenosis developed a 20% reduction in resting flow velocity. In all dogs, left anterior descending coronary flow reserve (measured by the increase in flow after injection of adenosine), remained unchanged over the time-course of left circumflex stenosis development. In contrast, left circumflex coronary flow reserve was significantly attenuated in all dogs between the second postoperative day and the final day of observation (Figure 1). The ratio of left anterior descending to left circumflex coronary reserve was markedly elevated in all experiments by the final day of monitoring, further demonstrating that coronary reserve in the Ameroid-constricted vessel was reduced as compared with reserve of the normal left anterior descending artery (Figure 1). This ratio was significantly greater in dogs with a severe left circumflex coronary artery stenosis than it was in dogs with moderate stenosis.

Desflurane and Hemodynamics

End-tidal concentrations of desflurane administered to dogs with moderate left circumflex coronary stenosis were 8.2% ± 1.1% and 12.7% ± 1.2%. Concentrations of 9.2% ± 0.7% and 12.5% ± 0.6% were administered to dogs with a severe stenosis. Systemic and coronary hemodynamic responses to desflurane in dogs with moderate or severe degree of left circumflex coronary artery stenosis are summarized in Tables 1 and 2. After left anterior descending coro-

Table 2. Hemodynamic Effects of Desflurane in Dogs With a Severe Left Circumflex Coronary Artery Stenosis

	Before occlusion	After occlusion	Desflurane (9.2%)	Desflurane (12.5%)	Desflurane (BP/HR) (12.5%)
Heart rate (beats/min)	103 ± 7[a]	124 ± 4	132 ± 5	113 ± 6	117 ± 3
Mean arterial pressure (mm Hg)	101 ± 4	104 ± 5	77 ± 6[a]	65 ± 6[a]	107 ± 5
Left ventricular systolic pressure (mm Hg)	134 ± 5	130 ± 6	101 ± 6[a]	90 ± 6[a]	118 ± 8[a]
Left ventricular end-diastolic pressure (mm Hg)	7 ± 1[a]	10 ± 1	17 ± 2[a]	19 ± 3[a]	26 ± 2[a]
$+dP/dt_{50}$ (mm Hg/s)	2220 ± 130	2090 ± 110	1660 ± 130[a]	1360 ± 130[a]	1000 ± 120[a]
LCCA diastolic blood flow velocity (Hz × 10^2)	37 ± 5	39 ± 5	40 ± 6	36 ± 6	39 ± 6
LCCA mean blood flow velocity (Hz × 10^2)	28 ± 4	28 ± 3	28 ± 6	25 ± 4	28 ± 4
LCCA segment shortening (%)	19.4 ± 2.9	18.4 ± 2.6	15.1 ± 2.8	14.1 ± 2.0[a]	10.6 ± 1.9[a]
LAD segment shortening (%)	16.7 ± 4.8[a]	4.5 ± 1.6	4.0 ± 1.9	3.5 ± 1.8	2.0 ± 1.5
Arterial pH	—	7.43 ± 0.01	7.41 ± 0.03	7.40 ± 0.02	—
Arterial P_{CO_2}	—	29 ± 1	28 ± 2	29 ± 1	—
Arterial P_{O_2}	—	88 ± 1	112 ± 7[a]	112 ± 4[a]	—

LCCA, left circumflex coronary artery; BP/HR, blood pressure and heart rate adjusted to "After occlusion" levels via partial aortic constriction and atrial pacing; LAD, left anterior descending coronary artery.

All values are expressed as mean ± SEM ($n = 6$).

Data in the "Before occlusion" and "After occlusion" groups were obtained in the awake state.

[a] Significantly different from "After occlusion" levels ($P < 0.05$).

Table 3. Conscious Control Myocardial Blood Flow in Dogs With Moderate or Severe Left Circumflex Coronary Artery Stenosis

	Moderate stenosis ($n = 6$)	Severe stenosis ($n = 6$)
Stenosis zone perfusion (% normal zone flow)	100 ± 7	83 ± 6[a]
Stenosis zone endo/epi	1.63 ± 0.19	1.15 ± 0.17[a]

Endo/epi, ratio of subendocardial to subepicardial blood flow.

Values are expressed as mean ± SEM.

[a] Significantly different from moderate stenosis group ($P < 0.05$).

nary occlusion, heart rate and left ventricular end diastolic pressure increased in all dogs, but mean arterial pressure increased only in dogs with moderate left circumflex stenosis (Table 1). In both the dogs with moderate and the dogs with severe stenosis, left circumflex diastolic and mean blood flow velocities and segment shortening in the left circumflex perfusion territory remained unchanged after left anterior descending coronary artery occlusion. Segment shortening in the occluded region, however, was markedly reduced in all dogs.

Desflurane produced concentration-dependent reductions in mean arterial and left ventricular systolic pressures, reductions similar in magnitude in dogs with a moderate and those with a severe left circumflex stenosis. After administration of desflurane, there was a significant increase in left ventricular end-diastolic pressure. The reduction in arterial pressure produced by desflurane was not accompanied by an increase in heart rate. Left ventricular dP/dt_{50} was decreased by desflurane and remained reduced below control when arterial pressure and heart rate were adjusted to conscious levels. Segment shortening in the left circumflex zone was significantly decreased in only the severe stenosis group during the high concentration of desflurane, but the decrease in function was observed in both groups when systemic hemodynamic conditions (arterial pressure and heart rate) present during the conscious state were restored with aortic constriction and atrial pacing. Left circumflex diastolic and mean coronary blood flow velocities and segment shortening in the occluded zone were unaffected by administration of desflurane.

Desflurane and Myocardial Perfusion

The distribution of coronary blood flow to normal, stenotic, and occluded zones in conscious, chronically instrumented dogs is summarized in Tables 3–5 and Figures 2 and 3. In all experiments, perfusion distal to the total left anterior descending coronary occlusion was reduced in the subepicardium, midmyocardium, and subendocardium below levels in the normal zone. Resting transmural myocardial blood flow distal to a severe stenosis but not a moderate stenosis also decreased below flow levels in the normal zone (Table 3). The ratio of flow between subendocardium and subepicardium (endo/epi) was

Table 4. Effects of Desflurane on Regional Myocardial Blood Flow (mL·min^{-1}·g^{-1}) in Dogs With a Moderate Left Circumflex Coronary Artery Stenosis

	Conscious	Desflurane (8.2%)	Desflurane (12.7%)	Desflurane (BP/HR) (12.7%)
Normal				
Subepicardium	0.81 ± 0.04	1.09 ± 0.17	1.07 ± 0.20	0.93 ± 0.08
Midmyocardium	1.46 ± 0.20	1.35 ± 0.11	1.31 ± 0.20	1.40 ± 0.11
Subendocardium	1.56 ± 0.26	1.35 ± 0.15	1.17 ± 0.14[a]	1.58 ± 0.16
Transmural	1.28 ± 0.16	1.26 ± 0.11	1.18 ± 0.16	1.30 ± 0.09
Stenotic				
Subepicardium	0.92 ± 0.16	0.97 ± 0.10	0.98 ± 0.19	0.83 ± 0.09
Midmyocardium	1.32 ± 0.19	1.06 ± 0.06	1.06 ± 0.12	1.15 ± 0.08
Subendocardium	1.60 ± 0.22	1.15 ± 0.09[a]	1.07 ± 0.20[a]	1.39 ± 0.15
Transmural	1.28 ± 0.18	1.06 ± 0.06	1.03 ± 0.14	1.12 ± 0.08
Occluded				
Subepicardium	0.22 ± 0.06	0.08 ± 0.03[a]	0.08 ± 0.02[a]	0.31 ± 0.08
Midmyocardium	0.12 ± 0.05	0.03 ± 0.01[a]	0.04 ± 0.02[a]	0.06 ± 0.02
Subendocardium	0.16 ± 0.05	0.07 ± 0.03[a]	0.09 ± 0.05[a]	0.10 ± 0.04
Transmural	0.16 ± 0.05	0.06 ± 0.01[a]	0.07 ± 0.02[a]	0.16 ± 0.04

BP/HR, blood pressure and heart rate adjusted to "Conscious" levels via partial aortic constriction and atrial pacing.
All values are expressed as mean ± SEM ($n = 6$).
[a] Significantly different from "Conscious" levels with a totally occluded left anterior descending and left circumflex coronary artery stenosis ($P < 0.05$).

Table 5. Effects of Desflurane on Regional Myocardial Blood Flow (mL·min^{-1}·g^{-1}) in Dogs With a Severe Left Circumflex Coronary Artery Stenosis

	Conscious	Desflurane (9.2%)	Desflurane (12.5%)	Desflurane (BP/HR) (12.5%)
Normal				
Subepicardium	0.92 ± 0.14	1.09 ± 0.14	1.08 ± 0.13	0.73 ± 0.11
Midmyocardium	1.28 ± 0.15	1.24 ± 0.13	0.92 ± 0.13[a]	1.08 ± 0.13
Subendocardium	1.37 ± 0.16	1.17 ± 0.13	0.81 ± 0.15[a]	1.24 ± 0.14
Transmural	1.19 ± 0.14	1.17 ± 0.12	0.84 ± 0.13[a]	1.01 ± 0.12
Stenotic				
Subepicardium	0.90 ± 0.14	0.96 ± 0.05	0.69 ± 0.09[a]	0.75 ± 0.06
Midmyocardium	1.06 ± 0.08	0.97 ± 0.15	0.78 ± 0.09[a]	1.07 ± 0.08
Subendocardium	0.92 ± 0.10	0.80 ± 0.18	0.66 ± 0.12[a]	1.01 ± 0.05
Transmural	0.96 ± 0.08	0.91 ± 0.12	0.71 ± 0.08[a]	0.94 ± 0.04
Occluded				
Subepicardium	0.22 ± 0.05	0.11 ± 0.03[a]	0.08 ± 0.03[a]	0.35 ± 0.07[a]
Midmyocardium	0.17 ± 0.03	0.04 ± 0.01[a]	0.04 ± 0.02[a]	0.14 ± 0.04
Subendocardium	0.21 ± 0.09	0.12 ± 0.08[a]	0.08 ± 0.06[a]	0.13 ± 0.06
Transmural	0.20 ± 0.06	0.09 ± 0.03[a]	0.07 ± 0.03[a]	0.21 ± 0.06

BP/HR, blood pressure and heart rate adjusted to "Conscious" levels via partial aortic constriction and atrial pacing.
All values are expressed as mean ± SEM ($n = 6$).
[a] Significantly different from "Conscious" levels with a totally occluded left anterior descending and left circumflex coronary artery stenosis ($P < 0.05$).

reduced distal to a severe left circumflex stenosis but not in areas distal to a moderate stenosis.

The influence of desflurane on regional myocardial blood flow in dogs with moderate or severe left circumflex coronary artery stenosis is summarized in Tables 4 and 5 and Figures 2 and 3. In dogs with a moderate degree of left circumflex stenosis, administration of desflurane significantly decreased blood flow distal to the total left anterior descending occlusion (Table 4). Blood flow was reduced in only the subendocardium of the normal and stenotic zones in the moderate stenosis group during desflurane anesthesia. In those experiments with a severe left circumflex stenosis, reductions in blood flow similar to those in the moderate stenosis group were produced by desflurane in the occluded zone (Table 5). In the severe stenosis group, perfusion was significantly decreased within the subepicardium, midmyocardium, and subendocardium of the stenotic zone and in midmyocardial and subendocardial regions of the normal zone during the high concentration of desflurane. On restoration of blood pressure and heart rate

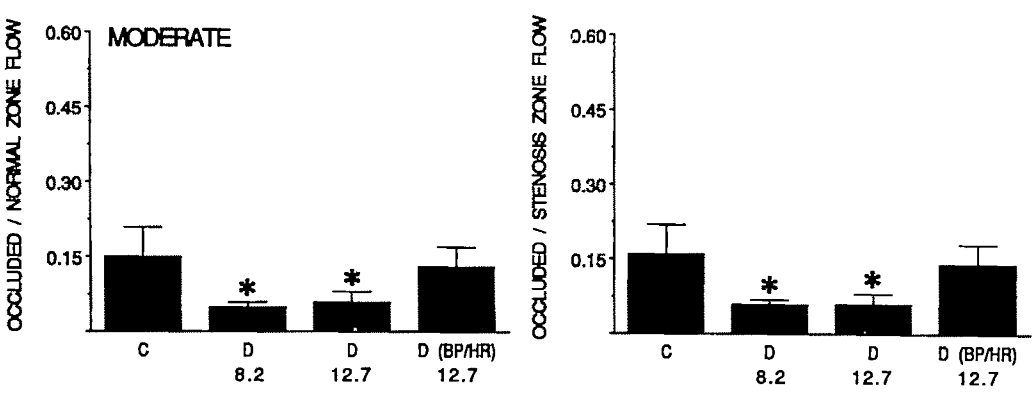


Figure 2. Ratio of occluded to normal zone or occluded to stenosis zone transmural myocardial blood flow during the conscious state (C), two concentrations of desflurane (D; 8.2% and 12.7%), and with blood pressure and heart rate returned to levels present in the conscious state (BP/HR) during the high concentration of desflurane in dogs with a *moderate* left circumflex coronary artery stenosis. *Significant ($P < 0.05$) difference from the conscious state (mean ± SEM data; $n = 6$).

to control levels during the high concentration of anesthetic using partial aortic constriction and atrial pacing, blood flow returned to control in all regions regardless of degree of stenosis severity (Tables 4 and 5). Ratios of blood flow between occluded and normal or occluded and stenotic zones were reduced by both concentrations of desflurane irrespective of the degree of left circumflex coronary stenosis (Figures 2 and 3). Desflurane produced no change in either ratio when atrial pressure and heart rate were artificially maintained at conscious control levels.

Discussion

The effect of desflurane on systemic and coronary hemodynamics and regional myocardial perfusion was investigated in a chronically instrumented canine model of multivessel coronary artery disease. All dogs were observed daily to determine the effects of progressive left circumflex stenosis development on coronary vascular reserve. When the left circumflex stenosis reached a moderate or severe level of constriction, the left anterior descending coronary artery was totally occluded to produce a model of multivessel coronary obstruction resulting in various degrees of regional ischemia. Administration of desflurane reduced coronary collateral perfusion when arterial pressure and heart rate were uncontrolled, but on restoration of conscious systemic hemodynamic conditions during anesthesia, collateral blood flow was maintained at control levels.

Desflurane is a new volatile anesthetic that may have clinical advantages over the presently used agents due in part to its ability to produce rapid induction and emergence (23–25), together with minimal metabolic breakdown (26) and limited generation of toxic by-products (27). The cardiovascular effects of desflurane have been initially described in several reports. A study performed in swine concluded that the cardiovascular depressive actions of desflurane were not distinguishable from those of isoflurane (12). However, when administered to humans desflurane appeared to reduce systemic vascular resistance and mean arterial pressure less than isoflurane (13). Desflurane maintained cardiac output at conscious levels at concentrations below 1.5 MAC at the expense of a significant increase in heart rate and reduction in stroke volume. In another study, variable concentrations of desflurane with 60% nitrous oxide were administered to volunteers. The inspired mixture of agents suppressed tachycardia but significantly decreased cardiac output, suggesting that desflurane may produce greater negative inotropic effects than an isoflurane-nitrous oxide combination (14). Whereas such studies have examined the hemodynamic effects of desflurane in normal animals (12,15,16) and humans (13,14,17), the action of this anesthetic in animal models of and humans with cardiovascular disease has yet to be examined. The present investigation is the first to focus on the action of desflurane on myocardial blood flow in a canine model of multivessel coronary artery disease.

The effects of halothane and isoflurane on myocardial perfusion in normal or obstructed coronary circulations have been previously reported (4,5,10,28). Isoflurane has been particularly scrutinized in such studies because of the coronary vasodilating activity that may be associated with coronary steal. Coronary steal has been defined as an elevation in blood flow to adequately perfused myocardium occurring at the expense of flow to a compromised, collateral-dependent region (29,30). Vasodilator-induced steal

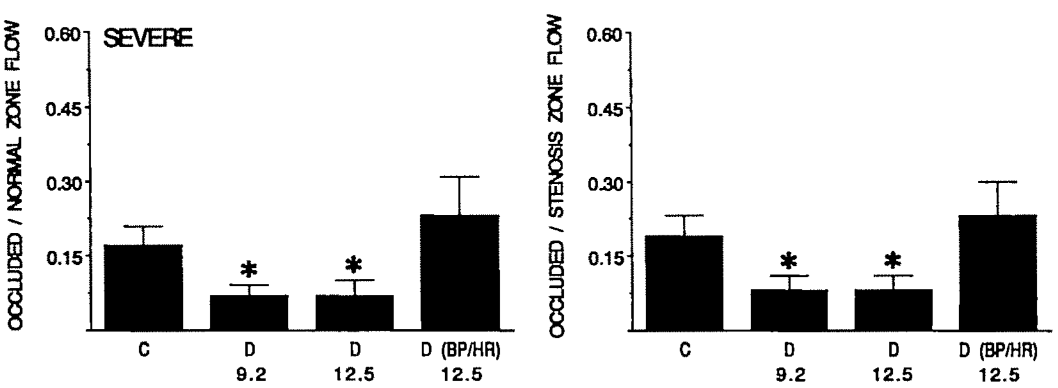


Figure 3. Ratio of occluded to normal zone or occluded to stenosis zone transmural myocardial blood flow during the conscious state (C), two concentrations of desflurane (D; 9.2% and 12.5%), and with blood pressure and heart rate returned to levels present in the conscious state (BP/HR) during the high concentration of desflurane in dogs with a *severe* left circumflex coronary artery stenosis. *Significant ($P < 0.05$) difference from the conscious state (mean ± SEM data; $n = 6$).

of collateral flow from a totally occluded region most readily occurs when a stenosis of the artery of origin of the collateral channels is present (31,32).

Desflurane, like isoflurane, may also possess coronary vasodilator activity. The present investigation sought to determine if desflurane produced vasodilation of normal zones and any redistribution of perfusion away from ischemic areas. A chronically instrumented canine model of coronary artery disease was utilized in which progressive constriction of the artery of origin of collaterals via an Ameroid occluder was monitored daily until a moderate or severe level of stenosis was achieved. After suitable stenosis development, the left anterior descending coronary artery was totally occluded to simulate a multivessel coronary artery disease condition. No acute surgery or baseline anesthesia was necessary before administration of desflurane, although antiarrhythmic agents were used to prevent sudden death after total left anterior descending coronary artery occlusion. Regional myocardial blood flow was measured during control conditions in the awake, unsedated state and after administration of each of two concentrations of desflurane. A final measurement of tissue flow was performed during the high concentration of anesthetic after diastolic arterial pressure and heart rate were adjusted to conscious levels.

At the conclusion of each experiment, myocardium from collateral-dependent regions distal to the hydraulic occluder, areas distal to the Ameroid-induced stenosis, and normal zones located proximally to both devices were selected for comparison of regional blood flow. The results demonstrated that desflurane had minimal if any vasodilator actions on tissue flow in normal areas. Furthermore, desflurane did not selectively redistribute myocardial perfusion from an ischemic region to a normal or stenotic zone. Reductions in blood flow to occluded and stenotic regions produced by desflurane were dependent on alterations of systemic hemodynamics. Perfusion in all regions was increased to levels present in the conscious state when arterial pressure and heart rate were restored using partial aortic constriction and atrial pacing to control postocclusion levels. Changes in the ratios of flow between occluded and normal or stenotic zones also suggested that desflurane does not decrease flow to any region preferentially or produce steal during a constant aortic pressure and heart rate. Lack of effect of desflurane on blood flow to collateral-dependent myocardium during control of systemic hemodynamics was also independent of the severity of the stenosis affecting the artery of origin of the coronary collaterals.

The lack of redistribution of perfusion away from subendocardium during desflurane anesthesia with a constant aortic pressure and heart rate occurred concomitantly with an increase in left ventricular end-diastolic pressure. Also, a significant increase in left ventricular end-diastolic pressure was observed with desflurane during a dose-dependent decrease in arterial pressure. The latter occurred during the pressure-dependent fall in collateral and stenotic zone blood flow and conceivably produced a net increase in ventricular wall stress. Such an increase in wall stress may lead to an increase in myocardial oxygen demand and may exacerbate ischemia.

A potential limitation of the protocol described in this investigation was that no efficacious coronary vasodilating agent (such as adenosine or dipyridamole) was administered to serve as a "positive control" and verify that coronary steal could occur in this model. However, a previous report from this laboratory has documented the validity of the preparation described in the present investigation in that adenosine was demonstrated to produce a marked coronary steal (11). In this study, adenosine increased perfusion of normal myocardium but decreased blood flow to the collateral-dependent region, which remained reduced during control of arterial pressure and heart rate. The effect of isoflurane on the present model was also shown to maintain perfusion of all myocardial zones when conscious systemic hemodynamics were restored regardless of left circumflex stenosis severity.

In summary, this investigation has demonstrated that desflurane anesthesia does not preferentially redistribute myocardial blood flow away from an ischemic region in a chronically instrumented canine model of multivessel coronary artery disease. Reductions in myocardial perfusion during desflurane anesthesia were found to be dependent on systemic arterial pressure. The results further demonstrated that when hypotension was corrected during desflurane anesthesia, blood flow to myocardium distal to a stenosis or total coronary artery occlusion was maintained at levels present in the conscious state regardless of the degree of coronary artery stenosis of the artery of origin of collaterals.

The authors extend their appreciation to John Tessmer, Doug Hettrick, and David Schwabe for their superb technical assistance. The authors are grateful for the secretarial assistance of Mimi Mick. The authors thank Anaquest (Madison, Wis.) for the use of an anesthesia machine and the generous supply of desflurane.

References

1. Tarnow J, Markshies-Hornung A, Schulte-Sasse U. Isoflurane improves the tolerance to pacing-induced myocardial ischemia. Anesthesiology 1986;64:147–56.
2. Khambatta HJ, Sonntag H, Larsen R, Stephan H, Stone JG, Kettler D. Global and regional myocardial blood flow and metabolism during equipotent halothane and isoflurane anesthesia in patients with coronary artery disease. Anesth Analg 1988;67:936–42.
3. Reiz S, Balfors E, Sorensen MB, Ariola S, Friedman A, Truedsson H. Isoflurane—a powerful coronary vasodilator in patients with coronary artery disease. Anesthesiology 1983;59:91–7.
4. Sivarajan M, Bashein G. Effect of halothane on coronary collateral circulation. Anesthesiology 1985;62:588–96.
5. Buffington CW, Romson JL, Levine A, Duttlinger NC, Huang AH. Isoflurane induces coronary steal in a canine model of chronic coronary occlusion. Anesthesiology 1987;66:280–92.
6. Cason BA, Verrier ED, London MJ, Mangano DT, Hickey RF. Effects of isoflurane and halothane on coronary vascular resistance and collateral myocardial blood flow: their capacity to induce coronary steal. Anesthesiology 1987;67:665–75.
7. Becker LC. Is isoflurane dangerous for the patient with coronary artery disease? (editorial). Anesthesiology 1987;66: 259–61.
8. Bollen BA, Tinker JH, Hermsmeyer K. Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. Anesthesiology 1987;66:748–52.
9. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
10. Hartman JC, Kampine JP, Schmeling WT, Warltier DC. Volatile anesthetics and regional myocardial perfusion in chronically instrumented dogs: halothane versus isoflurane in a single vessel disease model with enhanced collateral development. J Cardiothorac Anesth 1990;4:588–603.
11. Hartman JC, Kampine JP, Schmeling WT, Warltier DC. Alterations in collateral blood flow produced by isoflurane in a chronically instrumented canine model of multivessel coronary artery disease. Anesthesiology (in press).
12. Weiskopf RB, Holmes MA, Eger EI II, Johnson BH, Rampil IJ, Brown JG. Cardiovascular effects of 1653 in swine. Anesthesiology 1988;69:303–9.
13. Weiskopf RB, Cahalan MK, Yasuda N, et al. Cardiovascular actions of desflurane (I-653) in humans (abstract). Anesth Analg 1990;70:S426.
14. Cahalan MK, Weiskopf RB, Yasuda N, et al. Cardiovascular effects of desflurane and nitrous oxide in humans (abstract). Anesth Analg 1990;70:S46.
15. Weiskopf RB, Eger EI II, Holmes MA, et al. Epinephrine-induced premature ventricular contractions and changes in arterial blood pressure and heart rate during I-653, isoflurane, and halothane anesthesia in swine. Anesthesiology 1989;70: 293–8.
16. Weiskopf RB, Holmes MA, Rampil IJ, et al. Cardiovascular safety and actions of high concentrations of I-653 and isoflurane in swine. Anesthesiology 1989;70:793–8.
17. Yasuda N, Weiskopf RB, Cahalan MK, et al. Stimulation modifies the cardiovascular effects of desflurane in humans (abstract). Anesth Analg 1990;70:S445.
18. Lutz LJ, Milde JH, Milde LN. The cerebral hemodynamic and metabolic effects of I-653 in dogs (abstract). Anesth Analg 1990;70:S252.
19. Theroux P, Franklin D, Ross J, Kemper WS. Regional myocardial function during acute coronary artery occlusion and its modification by pharmacological agents in the dog. Circ Res 1974;35:896–908.
20. Domenech RJ, Hoffmann JI, Noble MI, Saunders KB, Henson JR, Subijanto S. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. Circ Res 1969;25:581–96.
21. Doorley BM, Waters SJ, Terrell RC, Robinson JL. MAC of I-653 in beagle dogs and New Zealand white rabbits. Anesthesiology 1988;69:89–91.
22. Steel RGD, Torrie JH. Principles and procedures of statistics: a biometrical approach. New York: McGraw-Hill, 1980:67–233.
23. Smiley R, Ornstein E. Emergence from desflurane anesthesia is more rapid than from isoflurane (abstract). Anesth Analg 1990;70:S378.
24. Eger EI II. Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 1987;66:971–3.
25. Eger EI, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. Anesth Analg 1987;66:977–82.
26. Yasuda N, Lockhart SH, Eger EI II, Weiskopf RB, Johnson BH, Faussolaki A. Desflurane, isoflurane, and halothane pharmacokinetics in humans (abstract). Anesth Analg 1990;70:S444.

27. Sutton TS, Koblin DD, Weiskopf RB, Gruenke LD, Waskell L, Eger EI II. Fluoride metabolites following prolonged exposure of volunteers to desflurane (abstract). Anesth Analg 1990;70: S398.
28. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. Anesth Analg 1984;63: 557–65.
29. Rowe GG. Inequalities of myocardial perfusion in coronary artery disease ("coronary steal"). Circulation 1970;42:193–4.
30. Cohen MV. Coronary collaterals—clinical and experimental observations. Mount Kisco, NY: Futura, 1985:394.
31. Becker LC. Conditions for vasodilator-induced coronary steal in experimental myocardial ischemia. Circulation 1978;57: 1103–10.
32. Gross GJ, Warltier DC. Coronary steal in four models of single or multiple vessel obstruction in dogs. Am J Cardiol 1981;48: 84–92.

Continuous Postoperative Regional Analgesia by Nerve Sheath Block for Amputation Surgery—A Pilot Study

Allan Fisher, MBChB, DObst RCOG, FFARCS, and Yitzhak Meller, MD

FISHER A, MELLER Y. Continuous postoperative regional analgesia by nerve sheath block for amputation surgery—a pilot study. Anesth Analg 1991;72:300–3.

A pilot study of continuous postoperative regional analgesia by nerve sheath block for lower limb amputation is presented. At the time of exposure of sciatic or posterior tibial nerve trunks during above- or below-knee amputations in 11 patients with ASA physical status III or IV, a catheter was introduced directly into the transected nerve sheath for continuous infusion of 0.25% bupivacaine at a rate of 10 mL/h for 72 h. Effective amputation stump analgesia was obtained, significantly reducing the need for on-demand narcotic analgesics during this time to a mean dose equivalent of 1.4 mg of morphine compared with a retrospective control group who received the equivalent of a mean dose of 18.4 mg of morphine ($P < 0.0001$). No complications related to the technique were observed. A follow-up of the group receiving continuous postoperative regional analgesia for up to 12 mo showed a total absence of phantom pain despite the presence of preoperative limb pain.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—continuous nerve sheath block. PAIN, POSTOPERATIVE—phantom limb. SURGERY, AMPUTATIONS—lower extremity.

Regional anesthesia significantly reduces the requirement for postoperative analgesic medication (1,2) and diminishes the incidence of long-term phantom pain after amputation (3). The prevention by regional anesthesia of afferent painful barrage of the spinal cord during operation prevents a state of spinal cord hyperexcitability responsible for aggravating the perception of postoperative pain (4).

The causes of phantom limb pain remain enigmatic, although several theories exist (5), and efforts to relieve established phantom pain with a wide variety of treatments have proved disappointing (6). Hence, a simple method of preventing immediate postoperative pain and long-term pain after limb amputation could be of great practical value.

We present a preliminary prospective study of continuous postoperative regional analgesia (CPRA) by nerve sheath block for lower limb amputation, achieved by continuous infusion of local anesthetic agent directly into the transected nerve sheath. Assessment of the immediate postoperative analgesic effect and follow-up of the occurrence of phantom limb pain are reported.

Methods

After approval by the Hospital Ethical Committee, informed consent was obtained from 11 consecutive oriented and cooperative patients, all ASA physical status III or IV, scheduled for lower limb amputation because of septic gangrene due to occlusive vascular disease; six patients suffered from diabetes mellitus. All patients had moderate to severe limb pain preoperatively for a period ranging from several weeks to months. Under general anesthesia, above-knee amputation was performed in four patients, and below-knee amputation in seven. Intraoperatively, the transected sciatic or posterior tibial nerve trunk was dissected out in the exposed above- or below-knee amputation stump, respectively; and the distal end of an 18-gauge epidural catheter was inserted 5 cm along the transected nerve trunk, then sutured in place to the nerve sheath and subcutaneous tissues with absorbable sutures. The proximal end of the catheter was led through the skin through a separate lateral incision and was sutured to the skin; all internal sutures were loose enough to allow easy withdrawal of the catheter at the end of its use. At

---

Received from the Division of Anesthesiology and Department of Orthopedic Surgery, Soroka Medical Center, and Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel. Accepted for publication October 12, 1990.

Address correspondence to Dr. Fisher, Division of Anesthesiology, Soroka Medical Center, Beersheva, Israel.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Postoperative Parenteral Narcotic Analgesics Administered to Continuous Postoperative Regional Analgesia and Control Groups and Their Equipotent Doses of Morphine

Name	Dose (mg)	Equipotent dose of morphine (mg)
Pentazocine	30–60[a]	10
Oxycodone	10–15[a]	10
Meperidine	75–100[a]	10

[a] In this study the upper dose in each range was taken as equipotent to 10 mg of morphine.

Table 2. Age Distribution of Patients in the Continuous Postoperative Regional Analgesia and Control Groups

	CPRA group			Control group			
Amputation	Mean	Range	*n*	Mean	Range	*n*	*P* value
Below knee	66.8	54–75	7	65.2	50–73	16	0.69
Above knee	77.8	72–83	4	73.5	69–80	4	0.32
Total	70.8	54–83	11	66.9	50–80	20	0.21

CPRA, continuous postoperative regional analgesia.
Patients' ages (means and ranges) are in years.

Table 3. Total Parenteral Narcotic Analgesics Administered in the First 72 Hours Postoperatively

	CPRA group			Control group			
Amputation	Mean	Range	*n*	Mean	Range	*n*	*P* value
Below knee	2.1	0–10	7	15.9	10–45	16	0.0015
Above knee	0		4	28.1	20–30	4	0.068
Total	1.4	0–10	11	18.4	10–45	20	0.0001

CPRA, continuous postoperative regional analgesia.
Mean and range are given as equivalent to milligrams of morphine.

this time (~30 min before the end of the operation), an initial dose of 20 mL of 0.25% bupivacaine was injected through a bacterial filter attached to the catheter's proximal end, and a 10-mL/h infusion of 0.25% bupivacaine was started. The operation was completed, and the wound closure was performed. Bupivacaine (0.25%) was infused through the filter at a constant rate of 10 mL/h for 72 h postoperatively after which the catheter was withdrawn. The patients were closely supervised for early signs of bupivacaine intoxication such as drowsiness, facial paresthesia, or visual or auditory disturbance.

During this time, patients received intramuscular injections of meperidine as required on demand from the nursing staff. The amount of postoperative analgesic administered was used as an index of pain experienced.

During hospitalization, and at monthly intervals for 6 mo and then every 3 mo for up to a year after amputation, these patients were questioned by the same surgeon for the presence of phantom pain or other complications. Phantom pain was defined as the presence of painful sensations referred to the lost body part (7), and the patient was specifically questioned about this at each postoperative visit.

A retrospective control group of 20 patients who had received only parenteral narcotic analgesics on demand postoperatively after lower limb amputation was studied for comparison. All patients had suffered from septic gangrene due to occlusive vascular disease, and eight were diabetic. This group was used for comparison with the CPRA group regarding the amount of postoperative analgesics administered on demand in the first 72 h. Table 1 shows the analgesics used and their ranges of doses equivalent to 10 mg of morphine (8). In this study, the upper dose in each range was taken as equivalent to 10 mg of morphine, and all analgesic doses were converted to equipotent doses of morphine to facilitate comparison.

As it was not possible to obtain reliable information regarding phantom pain from this retrospective group of controls, direct comparison of the incidence of phantom pain between CPRA and control group awaits a prospective randomized study.

Statistical analysis was performed with the SAS Statistical Analysis Package (SAS Institute Inc., Cary, N.C.). Comparison between means was performed using the Student's *t*-test assuming unequal variances. Fourfold tables were analyzed with the two-tailed Fisher's exact test.

Results

The CPRA and control groups were similar with regard to age (Table 2), to disease (septic gangrene due to peripheral vascular disease), and to operation performed (lower limb amputation). Table 2 shows means and ranges of patient ages in the CPRA and control groups (overall 70.8 and 66.9 yr, respectively; $P = 0.21$).

Table 3 shows the means and ranges of narcotic analgesics converted to equipotent doses of morphine administered parenterally on demand in the first 72 h postoperatively in the CPRA and control groups. The mean morphine equivalent requirement in the CPRA and control groups in below-knee amputation were 2.1 and 15.9 mg ($P = 0.0015$); in above-knee amputation, 0 and 28.1 mg ($P = 0.068$); and overall 1.4 and 18.4 mg ($P < 0.0001$), showing a highly significant reduction in narcotic analgesic requirement in the CPRA group.

Table 4. Length of Follow-up for Phantom Pain in the Continuous Postoperative Regional Analgesia Group

Length of follow-up	Amputation	No. of patients
2 mo	Above knee	2
1 yr	Below knee	7
1 yr	Above knee	2

No complications were observed as a result of the technique. Wound healing was good, no local or systemic infection occurred related to the catheter, and there were no clinical signs of bupivacaine intoxication. No patient required bladder catheterization as a result of the CPRA technique.

Follow-up of all 11 patients treated by CPRA showed total absence of phantom pain; two patients died after 2 mo and nine patients were observed for a year (Table 4). Two patients mentioned occasional paresthesia, which did not disturb them.

Discussion

This feasibility study shows CPRA by nerve sheath block during amputation operation to be a simple technique providing excellent postoperative amputation-stump analgesia and eliminating or significantly reducing the need for supplementary narcotic analgesics. This avoids the well-known side effects of this group of drugs, particularly in elderly patients with poor general condition frequently seen for amputation. The decrease in immediate postoperative pain in the 11 CPRA patients was also associated with the absence of phantom limb pain for up to 1 yr after amputation in all 11 patients, all of whom had suffered significant preoperative limb pain for weeks to months.

Phantom pain is a troublesome phenomenon occurring in up to 85% of amputees and is characteristically resistant to a variety of treatments (6). Early phantom pain is also associated with the presence of preoperative limb pain (9). A report by Bach et al. (3) represents an effort to prophylactically reduce phantom pain by administering epidural analgesia preoperatively for 3 days, with a reported reduction in phantom pain in the first year. Continuous postoperative regional analgesia by nerve sheath block appears to prevent occurrence of phantom pain, at least for a year, and is administered from the time of its initiation intraoperatively and continued during the postoperative period, hence saving the time necessary for preoperative treatment (3). In addition, none of the CPRA patients required bladder catheterization as a result of the technique itself or experienced other side effects associated with epidural analgesia, such as hypotension or reduced sensation and motor power.

No single cause has been found to satisfactorily explain phantom pain, and it seems likely that a complex multifactorial interaction operates involving peripheral nerves, central nervous system, and sympathetic system, with possible psychological overlay (5). Peripheral injury has been demonstrated to cause increased excitability of the spinal cord (10,11), and dorsal horn neuron response can be prolonged and increased by afferent C fiber stimulation (12). Peripheral nerve transection in particular results in afferent barrage that initiates spinal cord reflex excitability (13) with expansion of the receptive fields of dorsal horn neurons that respond to the nearest intact afferents (11). Wall (4) has suggested that the rationale of use of regional block to prevent bombardment of the central nervous system during operation lies in avoidance of spinal cord hyperexcitability and in reduction of postoperative pain. Reports of the effectiveness of local or regional anesthesia before operation in reducing the incidence and the severity of short- and long-term postoperative pain support this theory (1–3).

Continuous regional block has been described in the past both for the upper limb (14–17) and the lower limb (18,19) for intraoperative and postoperative use. Continuous postoperative regional analgesia by nerve sheath block after amputation is a method of continuous regional block of transected peripheral nerve that provides excellent analgesia during the duration of the block. Its mechanism of action in eliminating phantom pain for up to a year in the group studied may be related to modification of spinal cord excitability by prolonged block of peripheral afferent nociceptive impulses. As the technique involves administration of the block intraoperatively after amputation of the leg and transection of the nerves, peripheral injury has already occurred by the time the block is instituted. Hence, the situation is not identical to that suggested by Wall (4) and is supported by the evidence available (1–3) in which preoperative nerve block may prevent the occurrence of nociceptive bombardment of the central nervous system. In CPRA, it is possible that the prolonged block administered intraoperatively soon after the peripheral trauma of amputation and continued into the postoperative period may modify and reduce the hyperexcitability response of the spinal cord. This technique may be applicable intraoperatively to other nerve sheaths exposed by surgical dissection.

Satisfactory clinical analgesia of the amputation stump was obtained with CPRA by nerve sheath block of the sciatic nerve in above-knee amputation despite the fact that sensory innervation of the anterior aspect of the thigh comes from the femoral nerve. This, together with the large amount of bupivacaine solution infused, raises the question of the extent of spread of the local anesthetic solution and the extent of the block obtained. These and the resulting blood levels of bupivacaine remain to be investigated.

On the basis of this pilot study, CPRA appears to be a promising technique in amputation surgery because of the decreased need for postoperative narcotic analgesics and because of the absence for at least a year of phantom limb pain with which it is associated. Further detailed investigation is required, and to this end, a double-blind multicenter trial is planned.

We are grateful to Professor T. Gesztes and Dr. G. Gurman, Division of Anesthesiology; Professor S. Dekel, Department of Orthopedic Surgery; Dr. A. Shapiro, Department of General Surgery; all anesthetic and surgical colleagues who assisted in this study. We also thank Margaret Helfgott-Fisher for typing the manuscript.

References

1. McQuay HJ, Carroll D, Moore RA. Postoperative orthopedic pain—the effect of opiate premedication and local anesthetic blocks. Pain 1988;33:291–5.
2. Tverskoy M, Cozacov C, Ayache M, Bradley EL, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. Anesth Analg 1990;70:29–35.
3. Bach S, Noreng MF, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988; 33:297–301.
4. Wall PD. The prevention of postoperative pain. Pain 1988;33: 289–90.
5. Iacono RP, Linford J, Sandyk R. Pain management after lower extremity amputation. Neurosurgery 1987;20:496–501.
6. Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans. Results of a trial survey. Am J Phys Med Rehabil 1983;62:227–38.
7. Jensen TS, Krebs B, Nielsen J, Rasmussen P. Phantom limb, phantom pain and stump pain in amputees during the first six months following limb amputation. Pain 1983;17:243–56.
8. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics. 7th ed. New York: Macmillan 1985:505,521.
9. Jensen TS, Krebs B, Nielsen J, Rasmussen P. Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics, and relationship to preamputation limb pain. Pain 1985;21:267–78.
10. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature 1983;306:686–8.
11. Woolf CJ, Wall PD. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve injury. Neuroscience 1986;17:1199–206.
12. Cook AJ, Woolf CJ, Wall PD, McMahon SB. Expansion of cutaneous receptive fields of dorsal horn neurons following C-primary afferent fibre inputs. Nature 1987;325:151–3.
13. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J Physiol (Lond) 1984;356:443–58.
14. Ansbro FP. A method of continuous brachial plexus block. Am J Surg 1946;71:716–22.
15. DeKrey JA, Schroeder CF, Buechel DR. Continuous brachial plexus block. Anesthesiology 1969;30:332.
16. Manriquez RG, Pallares V. Continuous brachial plexus block for prolonged sympathectomy and control of pain. Anesth Analg 1978;57:128–30.
17. Rosenblatt RM, Pepitone-Rockwell F, McKillop MJ. Continuous axillary analgesia for traumatic hand injury. Anesthesiology 1979;51:75–6.
18. Rosenblatt RM. Continuous femoral anesthesia for lower extremity surgery. Anesth Analg 1980;59:631–2.
19. Dahl JB, Christiansen CL, Dangaard JJ, Schultz P, Carlsson P. Continuous blockade of the lumbar plexus after knee surgery. Anaesthesia 1988;43:1015–8.

Patient-Controlled Sedation During Epidural Anesthesia

Woo Young Park, MD, and Patricia A. Watkins, CRNA

PARK WY, WATKINS PA. Patient-controlled sedation during epidural anesthesia. Anesth Analg 1991;72:304–7.

The purpose of this study was to evaluate the feasibility and advantages or disadvantages, if any, of patient-controlled sedation compared with sedation administered by the anesthesiologist during surgical epidural anesthesia. Forty patients were divided at random into two groups with 20 patients in each group. Patients in group 1 received 0.5–1.0 mg intravenous midazolam and 25–50 μg intravenous fentanyl in increments administered by the anesthesiologist to achieve intraoperative sedation; patients in group 2 self-administered a mixture of midazolam (0.5 mg) and fentanyl (25 μg) in increments using an Abbott Lifecare PCA infuser to achieve sedation. Demographics of the patients, the types of surgery performed, doses of midazolam and fentanyl administered in a given period of time, and the level of sedation maintained during epidural anesthesia and surgery were similar in both groups. Patients in the self-administered group, however, rated their level of comfort during anesthesia and surgery higher than did those in the anesthesiologist-controlled sedation group. This could have been due to a positive psychological effect produced by allowing patients to feel that they have some control over their situation. The findings of this study indicate that patient-controlled sedation using a combination of midazolam and fentanyl is a safe and effective technique that provides intraoperative sedation ranked better by patients than that provided by anesthesiologists using the same drugs. More studies are, however, needed to determine the best choice of drug(s), the doses, the lock-out intervals, and the possible use of continuous infusion with patient-controlled sedation.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL ANESTHESIA. HYPNOTICS, PATIENT-CONTROLLED SEDATION.

Successful epidural anesthesia requires not only intraoperative relief of pain but also an adequately sedated, cooperative patient. To allay fear and anxiety and to ease any discomfort associated with the performance of the epidural block and/or the surgical procedure, sedatives and narcotics are often administered intravenously in the operating room by the anesthesiologist (1). It has been our clinical experience that, because of wide individual variations in response to sedatives and narcotics, over- or undersedation is not infrequent. In addition, there is considerable variation in the level of sedation desired by different patients. An occasional patient requests that he be fully awake during the entire procedure. Other patients request heavy sedation with total amnesia for the event.

In recent years, patient-controlled analgesia (PCA) has become popular for postoperative pain control (2,3). There is evidence that the pain can be better controlled by the self-administration of small, repetitive, on-demand, intravenous doses of narcotics using a PCA infuser than by the traditional timed intramuscular administration of these drugs (4–6). It has been also reported that midazolam can be given using a PCA infuser to provide anxiolysis in the intensive care unit (7). A logical extension of this form of analgesia or anxiolysis is to allow patients to find and maintain their own steady state of sedation by self-administration of sedatives and/or narcotics during surgery. This study was designed to evaluate the feasibility and advantages or disadvantages, if any, of patient-controlled sedation (PCS) compared with sedation provided by an anesthesiologist during surgery performed under epidural anesthesia.

Methods

Forty patients scheduled to have epidural anesthesia for proposed elective surgery of lower extremities or lower abdomen and who had no history of narcotic abuse were investigated. Patients were divided equally into two groups at random with 20 patients in

---

Supported in part by Abbott Laboratories.

Received from the V.A. Medical Center and the Department of Anesthesiology, Georgetown University Medical School, Washington, D.C. Accepted for publication October 16, 1990.

Address correspondence to Dr. Park, Chief of Anesthesiology, V.A. Medical Center, 50 Irving Street N.W., Washington, DC 20422.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

each group. For sedation during anesthesia and surgery, patients in group 1 were given midazolam and fentanyl administered intravenously in divided doses at the discretion of the anesthesiologist. Patients in group 2 self-administered a mixture of midazolam and fentanyl intravenously using a PCA infuser.

Permission to conduct this study was obtained from the hospital's research review committee. After obtaining informed consent, patients were premedicated with 5–10 mg diazepam and/or 5–10 mg morphine. Morphine was administered intramuscularly and diazepam was administered either orally or intramuscularly approximately 1 h before surgery. On arrival in the operating room, the degree of sedation from premedication was rated jointly by the anesthesiologist assigned to the case and by the investigator using the "Sedation Scale" (1–10, 1 = fully awake; 5 = moderate sedation: resting comfortably with eyes closed but responsive to verbal stimuli; 10 = heavy sedation: unresponsive to verbal stimuli but responsive to gentle tactile stimuli). An intravenous cannula was inserted and a blood pressure cuff, electrocardiogram electrodes, and a pulse-oxymetry probe were applied. If indicated, the anesthesiologist administered 0.5–1.0 mg midazolam and/or 25–50 μg fentanyl in increments intravenously in group 1 patients before performing the epidural block. Midazolam was administered for sedation, and fentanyl was used to treat pain (or discomfort). Patients in group 2, on the other hand, self-administered a mixture of midazolam and fentanyl in 2.5-mL increments (each milliliter containing 0.2 mg midazolam and 10 μg fentanyl) as desired using an Abbott Lifecare PCA infuser (Abbott Laboratories, North Chicago, Ill.). The PCA infuser was programmed to allow self-administration of 2.5 mL of the mixture of midazolam and fentanyl with a minimum of a 5-min obligatory lock-out interval between consecutive doses.

When the patient was adequately sedated, he or she was placed in the lateral decubitus position on a horizontal operating room table. A #17 Tuohy needle was introduced through the second or third lumbar intervertebral space, and the epidural space was identified using "loss of resistance" technique. With the bevel of the needle pointing cephalad, 3 mL of 1.5%–2.0% lidocaine or 0.5% bupivacaine, both with epinephrine (1:200,000), was injected. After 1 min, if there was no evidence of inadvertent subarachnoid or intravenous injection of the drug, an additional amount of the same local anesthetic was injected at the approximate rate of 1.0 mL/s. An epidural catheter was inserted if indicated, and the patient was then positioned for surgery. Oxygen (3 L/min) was administered by nasal cannula in the operating room.

Table 1. Demographics of the Study Patients

	Group 1 (*n* = 20)	Group 2 (*n* = 20)	*P*
Age (yr)	59.6 ± 16.7	56.3 ± 10.4	NS
Height (cm)	175.6 ± 8.1	172.5 ± 7.9	NS
Weight (kg)	73.5 ± 14.8	79.8 ± 13.9	NS

Values are expressed as mean ± SD.

Group 1, anesthesiologist-controlled sedation; group 2, patient-controlled sedation; NS, not significant.

Skin incision was made only after confirming the presence of an adequate level and intensity of epidural anesthesia for the proposed surgery. During the surgery, patients in group 1 had midazolam administered intravenously in increments for sedation and fentanyl to treat discomfort (or pain) as determined by the anesthesiologist. Patients in group 2 self-administered a mixture of midazolam and fentanyl using a preprogrammed Abbott PCA infuser. At the end of surgery the total doses of midazolam and fentanyl given were calculated and the overall adequacy of the sedation during surgery was rated jointly by the anesthesiologist assigned to the case and the investigator using the aforementioned sedation scale. The patient was observed for any of the following complications during the study: (a) respiratory rate <6 breaths/min; (b) oxygen saturation <90% when nasal oxygen was administered at 3 L/min; (c) hypotension (systolic pressure <70 mm Hg); (d) nausea or vomiting; (e) restlessness and excitement; and (f) headache.

On the first postoperative day patients were asked to rate the overall comfort they had experienced in the operating room using the "Comfort Scale" (1–10, 1 = very uncomfortable; 5 = moderately comfortable; 10 = very comfortable). The degrees of the sedation and comfort were compared statistically between the two groups using ridit analysis (8) and other results using unpaired Student's *t*-test. Differences were considered to be statistically significant when the probability value was <0.05.

Results

Epidural anesthesia was adequate for the surgery in all 40 patients. Demographics of the patients and the types of surgery performed were similar in both groups (Tables 1 and 2). The level of sedation from premedication, doses of midazolam and fentanyl administered in a given period of time, the level of sedation maintained during anesthesia and surgery, and the duration of anesthesia and surgery were also

Table 2. Types of Surgery Performed During the Study

	Number of patients	
	Group 1 (n = 20)	Group 2 (n = 20)
Orthopedic hip/knee	9	7
Urologic prostate/urethra	4	7
Inguinal hernia repair	3	5
Vascular, lower extremities	4	1

Group 1, anesthesiologist-controlled sedation; group 2, patient-controlled sedation.

Table 3. Comparison of Clinical Data Between Two Groups of Patients

	Group 1 (n = 20)	Group 2 (n = 20)	P
Median Sedation Scale (1–10) after premedication	2.0	3.0	
(mean ridit score)	(0.48)	(0.51)	NS
Midazolam (mg)	3.3 ± 1.5	3.6 ± 2.5	NS
(range)	(1–8.5)	(0–10)	
Fentanyl (mg)	0.12 ± 0.05	0.18 ± 0.13	NS
(range)	(0.05–0.2)	(0–0.5)	
Duration of anesthesia and surgery (min)	196.4 ± 69.4	218.4 ± 112.9	NS
Median Sedation Scale (1–10) during surgery	5.5	6.0	
(mean ridit score)	(0.44)	(0.55)	NS
Median Comfort Scale (1–10) during surgery	8.0	10.0	
(mean ridit score)	(0.31)	(0.59)	<0.01

Values are expressed as mean ± SD. Group 1, anesthesiologist-controlled sedation; group 2, patient-controlled sedation; NS, not significant.

similar in both groups (Table 3). Patients in the PCS group, however, rated their level of comfort during anesthesia and surgery higher than did the patients in the anesthesiologist-controlled sedation group (Table 3). There were wide individual variations in the level of sedation maintained by patients within the PCS group. One patient in each group developed hypotension (systolic pressure <70 mm Hg) after epidural injection of the local anesthetic, which was corrected by an intravenous administration of 10–20 mg ephedrine. Despite the administration of oxygen (3 L/min) by nasal cannula, oxygen saturation decreased below 90% from an initial level of 96% in one patient in the PCS group after self-administration of 2.5 mg midazolam and 125 μg fentanyl. Oxygen saturation in this patient increased to 97% when oxygen (3 L/min) was administered by mask.

Discussion

Despite the fact that comparable doses of midazolam and fentanyl were used in both groups, patients in the PCS group indicated by their ratings on the comfort scale that they were more comfortable intraoperatively than patients to whom the drugs were administered at the discretion of the anesthesiologist. It seems likely that this difference could be attributed to the positive psychological effect of allowing the patients to feel that they have some control over their situations. The majority of the patients in the PCS group liked the idea of being allowed to find and maintain the level of sedation themselves.

The level of sedation provided by the anesthesiologist was most often moderate and similar in all patients. On the other hand, the level of sedation maintained by patients in the PCS group showed wide individual variations. Whereas some patients stayed fully awake, not using any sedatives, others pressed the button of the infuser until they fell asleep and pressed the button whenever they woke up from the sleep. It is, however, important to note a "fail-safe" feature in that the administration of an overdose was prevented by the inability of the patient to activate the infuser when asleep from heavy sedation.

In one patient in the PCS group, oxygen saturation decreased to 90% after self-administration of a combination of midazolam and fentanyl without any significant changes in blood pressure and/or respiratory rate; this decrease in saturation was corrected by administration of oxygen (3 L/min) by mask. Both midazolam and fentanyl are known to depress respiration (9–12). It has been reported that sympathetic blockade during epidural anesthesia attenuates the cardiovascular response to severe hypoxia (13), and that the respiratory depression (hypoxia and hypercarbia) produced by intravenous administration of sedatives and/or narcotics may have been responsible in one study for the cardiac arrests that occurred during spinal anesthesia (14). We recommend, therefore, that oxygen saturation be monitored whenever sedatives and/or narcotics are administered intravenously during epidural or spinal anesthesia.

The ideal PCS agent(s) would be drugs with rapid onset and moderate duration of action without adverse side effects. The combination of midazolam and fentanyl has an onset 2–3 min after intravenous administration and a duration of approximately 30–60 min, which we considered ideal. However, the possibility of respiratory depression is always present with this combination of drugs, even though it is a rare occurrence. This respiratory depression (often accompanied by arterial desaturation) is believed to be due to fentanyl (15). The question is, then, "Should we use fentanyl in addition to midazolam?" It has been our clinical impression that with a successful regional anesthesia and a short surgical procedure, midazolam provides adequate sedation. However, when regional anesthesia is not complete and the patient retains some pain perception or when the surgical procedure lasts longer than 2–3 h, the patient tends to become restless with midazolam sedation only. Lying in one position for an extended time results in the unblocked parts of the body becoming a source of discomfort and restlessness. In this situation, addition of a narcotic such as fentanyl is desirable.

In summary, the findings of the study indicate that PCS, using a combination of midazolam and fentanyl, is a safe and effective technique for intraoperative sedation that provides what patients consider to be sedation better than that provided by an anesthesiologist. However, more studies are needed to determine the best choice of the drug(s), the doses, the lock-out intervals, and the possible use of a continuous infusion with PCS.

We thank Kelvin K. Lee, PHD, for his valuable assistance with data analysis.

References

1. Philip BK. Supplemental medication for ambulatory procedures under regional anesthesia. Anesth Analg 1985;64:1117–25.
2. White PF. Use of patient-controlled analgesia for management of acute pain. JAMA 1988;259:243–7.
3. Tamsen A, Hartvig P, Dahlstrom B, et al. Patient-controlled analgesia therapy in the early postoperative period. Acta Anaesthesiol Scand 1979;23:462–70.
4. Kay B. Postoperative pain relief—use of an on-demand analgesia computer (ODAC) and a comparison of the rate of use of fentanyl and alfentanil. Anaesthesia 1981;36:949–51.
5. Sechzer PH. Studies in pain with analgesic demand system. Anesth Analg 1971;50:1–10.
6. Keeri-Szanto M, Heaman S. Postoperative demand analgesia. Surg Gynecol Obstet 1972;134:647–51.
7. Loper KA, Ready LB, Brody M. Patient-controlled anxiolysis with midazolam. Anesth Analg 1988;67:1118–9.
8. Bross IDJ. How to use ridit analysis. Biometrics 1958;14:18–38.
9. Foster A, Morel D, Bachman M, Gemperle M. Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study. Anesth Analg 1983;62:920–4.
10. Gross JB, Zebrowski ME, Carel WD, Gardner S, Smith TC. Time course of ventilatory depression after thiopental and midazolam in normal subjects and in patients with chronic obstructive pulmonary disease. Anesthesiology 1983;58:540–4.
11. Becker LD, Paulson BA, Miller RD, Severinghaus JW, Eger EI II. Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. Anesthesiology 1976;44:291–6.
12. Bailey PL, Streisand JB, East KA, et al. Differences in magnitude and duration of opioid-induced respiratory depression and analgesia with fentanyl and sufentanil. Anesth Analg 1990;70:8–15.
13. Peters J, Kutkuhn B, Medert HA, Schlaghecke R, Schuttler J, Arndt JO. Sympathetic blockade by epidural anesthesia attenuates the cardiovascular response to severe hypoxia. Anesthesiology 1990;72:134–44.
14. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. Anesthesiology 1988;68:5–11.
15. Tucker MR, Ochs MW, White RP Jr. Arterial blood gas levels after midazolam or diazepam administered with or without fentanyl as an intravenous sedative for outpatient surgical procedures. J Oral Maxillofac Surg 1988;44:688–92.

308 ANESTH ANALG
1991;72:308–15

Role of Experience in the Response to Simulated Critical Incidents

Abe DeAnda, MD, and David M. Gaba, MD

DEANDA A, GABA DM. Role of experience in the response to simulated critical incidents. Anesth Analg 1991;72:308–15.

Eight experienced anesthesiologists (faculty or private practitioners) were presented with the same simulated critical incidents that had previously been presented to 19 anesthesia trainees. The detection and correction times for these incidents were measured, as was compliance with Advanced Cardiac Life Support (ACLS) guidelines during cardiac arrest, and the occurrence of unplanned incidents. Experienced personnel tended to react more rapidly than did trainees, but differences between second-year anesthesia residents (CA2) and experienced anesthesiologists were not statistically significant. There was a high variability in performance between incidents and within each group. Unplanned errors and management flaws still occurred with experienced subjects.

The response to incidents during anesthesia is a complex process that involves multiple levels of cognitive activity and is vulnerable to error regardless of experience. Most trainees seemed to acquire adequate response routines by the end of the CA2 year. Formal reasoning appeared to play a minor role in responding to intraoperative events, but the exact nature of the anesthesiologist's cognition remains to be thoroughly investigated.

Key Words: ANESTHESIOLOGISTS, EXPERIENCE AND RESPONSES TO CRITICAL INCIDENTS. EDUCATION, SIMULATORS—experience and responses to critical incidents.

The response of the anesthesiologist to undesirable events during anesthesia is a critical factor in protecting the anesthetized patient. Cooper et al. stated (1) that anesthesiologists act as though "risk management depends almost solely on the anesthetist's ability to react instinctively and flawlessly every time a problem arises." We have previously reported that anesthesia trainees do not always act instinctively and flawlessly when confronted with simulated critical incidents (2), and that they cause or encounter a number of additional incidents in the course of managing the simulated patient (3). In this study we investigated the response of fully trained anesthesiologists to the same case scenario and the same critical incidents previously confronted by trainees. The results of this study and their comparison with those of the trainee studies should provide insights into the role of experience in handling critical incidents, as well as the common limitations of human decision making regardless of experience.

Method

Members of the full-time faculty and voluntary clinical faculty (private practitioners) of the Anesthesia Departments, Stanford University Hospital and Palo Alto Veterans Administration Medical Center, were invited to participate in this study. Eight volunteers (five faculty, three private practitioners) gave written informed consent (as approved by the Human Subjects Committee) and participated over a 2-mo period. All volunteers were "generalists" whose practice was not limited to specific subspecialties, and whose practice included anesthesia for cardiovascular surgery. The average level of postresidency experience was 15.8 yr (range, 7–35 yr). Because we were interested in comparing these experienced practitioners with the resident subjects of the prior investigations (2,3), we used the same CASE 1.2 simulator (4), and the same scenario involving a 1.5–2-h head-and-neck procedure. As previously described, the scenario included six planned intraoperative events:

Supported in part by a grant from the Anesthesia Patient Safety Foundation, and by the Veterans Administration. Dr. DeAnda was supported in part by a fellowship from the Commonwealth Fund.

Presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 1990.

Received from the Department of Anesthesia, Stanford University School of Medicine and Anesthesia Service, Palo Alto Veterans Administration Medical Center, Palo Alto, California. Accepted for publication October 16, 1990.

Address correspondence to Dr. Gaba, Anesthesia Service, 112A, Palo Alto VAMC, 3801 Miranda Avenue, Palo Alto, CA 94304.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

short airway hoses, endobronchial intubation secondary to head manipulation, intravenous (IV) line occlusion, acute atrial fibrillation, airway disconnection, and ventricular fibrillation.

The CASE 1.2 simulator has previously been described in detail (4). In brief, the simulator uses a real operating room including fully functional patient monitors. An intubation/thorax mannequin is used as the patient and includes an arm with palpable veins for intravenous access. A central computer is used to control the simulator, with inputs to the monitors being predetermined from a script and altered in real-time by the simulator operator. Subjects were instructed to "think aloud," and a videocamera was used to tape the simulation as well as the debriefing session that immediately followed it.

Data Collection

The response times for the detection and initiation of corrective action for each planned event were recorded by reviewing the videotapes. Detection was defined as the time from the onset of the event until the subject's first observation that an unexpected event had occurred. We relied on the subject's verbal observation in most cases. However, in instances where the subject did not "think aloud" sufficiently well, we considered detection to occur when the following two criteria were met: (a) the subject appeared to begin a context-appropriate action (for instance, looking at the electrocardiogram [ECG] monitor during atrial fibrillation), and (b) during the debriefing session we were able to verify the reason for the action. The correction time was defined as the time from the onset to initiating the performance of one of the predefined correction criteria related to that event. The subject verbally acknowledged the reason for the action either during simulation or retrospectively during debriefing. If a predefined appropriate corrective action was performed, credit was given whether or not the correct diagnosis had been made. The information and methods used by the subject in making the correct diagnosis were also recorded where possible. The latency time was calculated as the difference between the detection time and the correction time.

Unplanned Incidents

The recording method used with the CASE simulator has been previously shown to be a sensitive means of identifying inadvertent events during simulation (3). A modified critical incident technique (5) was used to categorize these occurrences. Criteria formulated in our earlier study (3) were used to categorize unplanned incidents as due to human error, equipment failure, unknown cause, or fixation error. As we previously described (3), fixation errors are a distinct type of human error involving persistent fixation of attention away from the most critical problem.

Analysis

The data were stratified by level of anesthesia training (first-year anesthesia resident [CA1], second-year anesthesia resident [CA2], and experienced). For statistical analysis, the eight experienced subjects were considered a single group, although Figure 1 shows them separated into faculty and private practitioner subgroups. The number of individuals in each subgroup was too small to allow hypothesis testing. The data were analyzed for each event using the F_{max}-test of homogeneity of variances (6). The nonparametric Kruskal-Wallis test was used to compare groups on a particular event where variances between groups were found to be heterogeneous. A one-way analysis of variance was performed where variances remained homogeneous across groups for the event analyzed. The distribution of each category of unplanned incident, as well as the results from the short airway hose planned event, was analyzed using the R × C tests of independence with Williams' correction (6). Significance was considered at $P < 0.05$.

Results

Response to Planned Incidents

Short airway hoses. One experienced subject did not recognize the need for longer breathing circuit hoses before turning the operating room table 180°. In that case the subject recognized the need for longer hoses less than 30 s after initiating the turn, thereby making the likelihood of an adverse patient outcome low. These results were not statistically different from results obtained in the resident groups, although 9 of 19 residents did *not* recognize the need before turning the table.

Endobronchial intubation. A single experienced practitioner failed to detect the endobronchial intubation, even after noting asymmetrical breath sounds on auscultation, a decrease in tidal volume, and an increase in end-tidal carbon dioxide. Instead, this

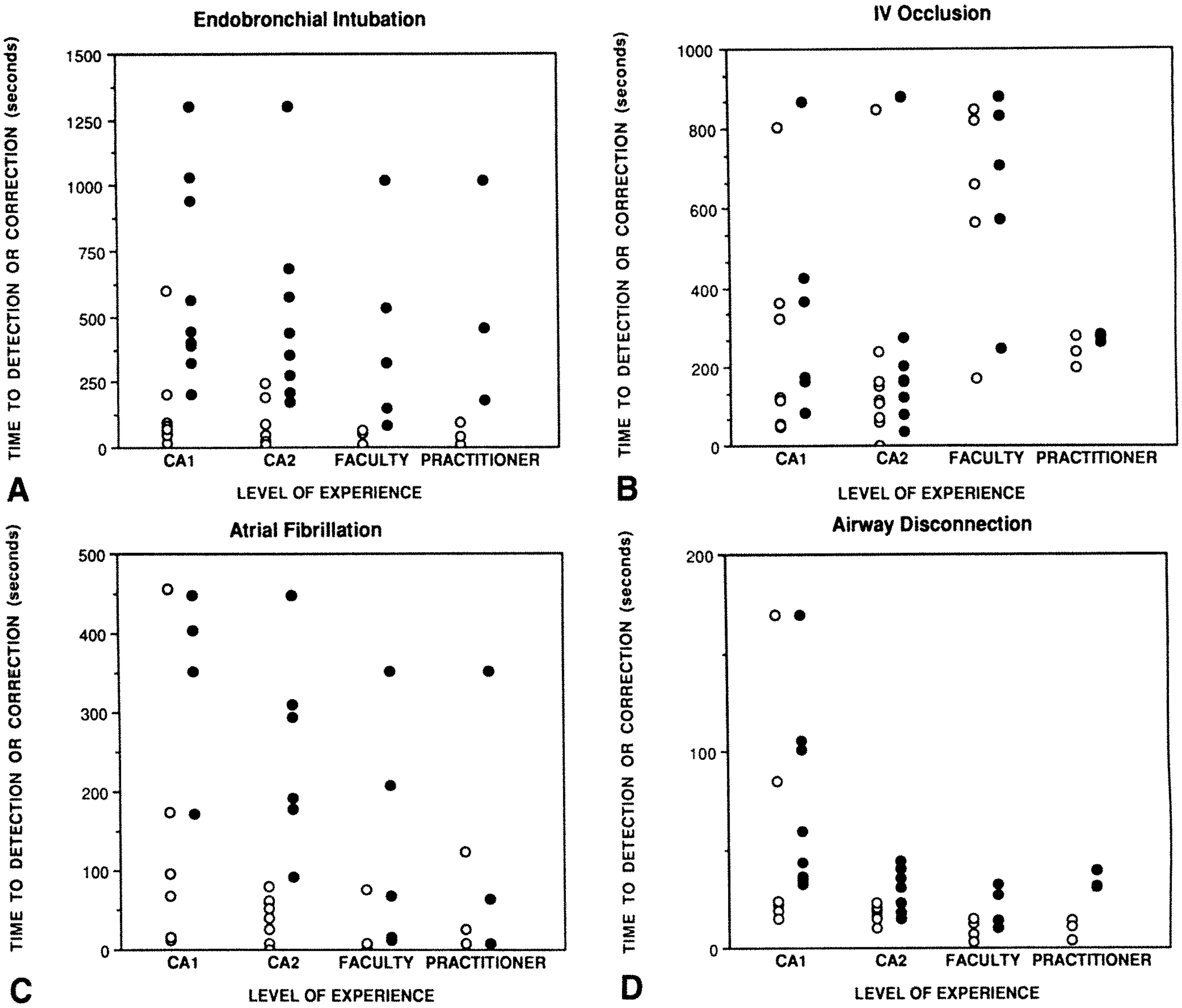


Figure 1. Detection time (*open circles*) and correction time (*filled circles*) for four planned incidents (A—endobronchial intubation; B—IV line occlusion; C—atrial fibrillation; D—airway disconnection). Each subject is shown stratified by level of anesthesia experience. Subjects with similar response times will overlap and appear as a single circle. Note that each incident has a different scale for response times. CA2 residents and experienced anesthesiologists responded more rapidly than did CA1 residents, but experienced personnel did not respond significantly faster than did CA2 residents. There was no apparent systematic difference between faculty and private practitioners.

anesthetist chose to treat the patient for bronchospasm, despite repeated assurances from the simulation director that the asymmetric breath sounds were not an artifact of the mannequin. Subjects who recognized endobronchial intubation used three techniques: three subjects noted a change in breath sounds via the esophageal stethoscope, two subjects observed an increase in the peak respiratory pressure, and two subjects noted an acute decrease in tidal volume (caused by the higher peak inspiratory pressure). Four of the subjects confirmed the diagnosis by auscultation of the chest; the other three relied on direct observation of the tube placement and a trial of repositioning the tube.

The response times for endobronchial intubation are shown in Table 1 and Figure 1A. The variances between groups were homogeneous except in the case of detection time, and the differences between groups were not statistically significant.

Intravenous line occlusion. Three of the eight subjects detected the occluded IV line before the detection of the next event (atrial fibrillation). The juxtaposition of these two events required a functional IV

Table 1. Detection and Correction of Planned Endobronchial Intubation

Level of training	Detection time (s)	Correction time (s)	Latency time (s)
CA1	137 ± 180	622 ± 376	485 ± 341
CA2	72 ± 90	484 ± 347	412 ± 350
Experienced	46 ± 32	471 ± 370	425 ± 360

CA1, first-year clinical anesthesia residents; CA2, second-year clinical anesthesia residents; experienced, full-time anesthesia faculty or private practitioners.

Table 2. Detection and Correction of Planned Intravenous Line Occlusion

Level of training	Detection time (s)	Correction time (s)	Latency time (s)
CA1	281 ± 298	484 ± 345	203 ± 245
CA2	191 ± 241[a]	244 ± 247	53 ± 32
Experienced	474 ± 284[a]	509 ± 273	35 ± 26

CA1, first-year clinical anesthesia residents; CA2, second-year clinical anesthesia residents; experienced, full-time anesthesia faculty or private practitioners.

[a] $P < 0.05$, CA2 versus experienced.

Table 3. Detection and Correction of Planned Atrial Fibrillation

Level of training	Detection time (s)	Correction time (s)	Latency time (s)
CA1	176 ± 199	407 ± 89[a]	231 ± 180
CA2	39 ± 26	318 ± 140[a]	279 ± 143[a]
Experienced	31 ± 45	135 ± 149	104 ± 113

CA1, first-year clinical anesthesia residents; CA2, second-year clinical anesthesia residents; experienced, full-time anesthesia faculty or private practitioners.

[a] $P < 0.05$ versus experienced.

Table 4. Detection and Correction of Planned Airway Disconnection

Level of training	Detection time (s)	Correction time (s)	Latency time (s)
CA1	25 ± 23[a]	72 ± 46[b]	47 ± 43[c]
CA2	17 ± 4	32 ± 9	15 ± 6
Experienced	9 ± 5	28 ± 10	18 ± 10

CA1, first-year clinical anesthesia residents; CA2, second-year clinical anesthesia residents; experienced, full-time anesthesia faculty or private practitioners.

[a] $P < 0.005$ versus experienced.

[b] $P < 0.001$ versus CA2 and experienced.

[c] $P < 0.025$ versus CA2 and experienced.

line before the administration of intravenous medications for the treatment of atrial fibrillation. Two of the subjects detected the occlusion only after attempting to administer intravenous medication for the treatment of atrial fibrillation and hypotension. Surprisingly, three of the subjects did not detect the occlusion until the cardiac arrest despite attempting to treat the intervening atrial fibrillation with intravenous medication.

Table 2 and Figure 1B show the response times for the IV line occlusion. The variances were homogeneous except for the latency time. There was a significant ($P < 0.05$) difference when comparing detection times between the CA2 group and the experienced group. The comparison of latency periods, although not statistically significant, did show a trend toward significance ($P = 0.068$) when comparing the CA1 group with the CA2 and experienced groups.

Atrial fibrillation. Seven of the subjects detected and correctly diagnosed the acute onset of atrial fibrillation. Six of these subjects initially detected this event by the change in ECG waveform on the patient monitor. One subject first detected the arrhythmia when he noted intermittent sensing of the pulse by the pulse oximeter and subsequently confirmed the diagnosis using the ECG monitor. The remaining subject noted an abnormal rhythm on the ECG monitor, but attributed it to monitor artifact. The treatment plan for atrial fibrillation was either verapamil or observation. No one utilized β-blockade, digoxin, vasopressors, or cardioversion.

Table 3 and Figure 1C show the response times for acute atrial fibrillation. The variances were homogeneous except in the case of detection time. There was a significant difference in correction times between the residents and experienced subjects, as well as the latency times between the CA2 group and the experienced group. The nonparametric comparison of detection times showed a tendency toward significance ($P = 0.075$) in comparing the CA1 group with the CA2 and experienced groups.

Airway disconnection. All subjects noted the airway disconnection, with the first signal in all cases being the low airway pressure alarm. Although there was some confusion as to which alarm was sounding, all subjects responded quickly and correctly.

Table 4 and Figure 1D show the response times for airway disconnection. The variances were heterogeneous in all cases. There was a significant difference between the CA1 group and the experienced group in the detection times, a significant difference between the CA1 group and the CA2 and experienced groups in the correction times, and a significant difference between the CA1 group and the CA2 and experienced groups in the latency time results.

Table 5. Detection and Correction of Planned Cardiac Arrest, ACLS Compliance

Level of training	Detection time (s)	Compliance with ACLS guidelines (*n*)		
		Perfect	Minor	Major
CA1	10 ± 5[*]	2	2	6
CA2	4 ± 2	1	3	5
Experienced	4 ± 4	0	5	3

CA1, first-year clinical anesthesia residents; CA2, second-year clinical anesthesia residents; experienced, full-time anesthesia faculty or private practitioners.

[*] $P < 0.005$ versus CA2 and experienced.

Cardiac arrest. All subjects detected and diagnosed the cardiac arrest. Correction time was always virtually simultaneous with detection and diagnosis. Despite quick recognition of the ventricular arrhythmia, some subjects departed substantially from established ACLS resuscitation protocols. One faculty subject never considered defibrillating the patient, and one private practitioner started with an external defibrillation energy of 10 J and repeatedly used low energy levels before recognizing his mistake.

Table 5 lists the detection times for the detection of ventricular fibrillation as well as the ACLS compliance. The variances were heterogeneous, and the difference between the CA1 group and the CA2 and experienced groups was significant. The distribution of ACLS compliance was not found to be significantly different between groups.

Unplanned Incidents

We documented 40 *unplanned* events during the eight simulations. Of the 40 incidents, 26 were considered simple incidents (minimal likelihood of patient compromise) and 14 were considered critical (high likelihood of patient compromise if not detected and corrected) using the criteria previously developed (3). The postresidency group averaged five unplanned events per case, compared to 7.9 and 5.9 for the CA1 and CA2 groups, respectively. The difference between the CA1 and the postresidency groups was statistically significant. Table 6 shows the overall distribution of unplanned incidents, which was significant only when comparing the CA1 group with the CA2 group. The *t*-test comparing each class of errors did not reveal a significant difference in the rate of occurrence in human and fixation errors, but there was a difference ($P = 0.028$) between the CA1 group and experienced group in the rate of occurrence of unknown errors, and between the CA2 and experienced groups in the rate of occurrence of equipment failures ($P = 0.045$) and unknown errors ($P = 0.031$).

Human errors. A total of 27 human errors were observed. Ventilator errors included one crossover error in switching from bag to mechanical ventilation, and two occasions of incorrect ventilator settings that created alarm conditions. One of the drug administration errors occurred when the subject stated repeatedly that the anesthesia plan included isoflurane as the volatile agent, but then inadvertently administered halothane and did not quickly recognize the mistake. Airway management errors included two unplanned endobronchial intubations, one accidental extubation, one accidental disconnection, and one major cuff leak. Intravenous fluid management errors occurred only with one subject and were related, as the subject accidentally placed the stopcock in the wrong position causing an attached syringe to fill with IV fluid. Shortly thereafter he recognized the error, but only after the IV fluid had stopped flowing. He increased the IV rate to make up for the approximately 4 min during which the patient was not receiving fluids. However, he did not remember to decrease the flow until the patient had received nearly 1 L of saline. Monitor errors tended to be due to unfamiliarity with the operation of the specific model of pulse oximeter and of mass spectrometer.

Equipment failures. There were three equipment failures. The first was a failure of a laryngoscope light after the subject had correctly checked it before the start of the case. The other failures were a stuck ventilator pressure valve (i.e., "pop-off" valve), and a defective IV needle that resulted in a delay in providing an IV medication.

Fixation errors. We recorded 10 fixation errors in the eight subjects. Three of the subjects fixated excessively on the patient's initial oxygen saturation of 95% while breathing room air despite a patient history of tobacco abuse. Seven subjects became fixated on the intermittent sensing activity of the pulse oximeter during atrial fibrillation, in each case persistently searching for an electromechanical cause of the irregular sensing even after identifying the arrhythmia.

Discussion

This study, combined with our two previous reports (2,3), represents the only comparative study of the

Table 6. Distribution of Unplanned Incidents by Type

Level of training	Human error	Equipment failure	Fixation error	Unknown cause	Total
CA1	57 (72.2%)	4 (5.1%)	12 (15.2%)	6 (7.6%)[a]	79[b]
CA2[c]	30 (56.6%)	0 (0.0%)[d]	15 (28.3%)	8 (15.1%)[a]	53
Experienced	27 (67.5%)	3 (7.5%)	10 (25.0%)	0 (0.0)%	40

CA1, first-year clinical anesthesia residents; CA2, second-year clinical anesthesia residents; experienced, full-time anesthesia faculty or private practitioners.

Percentages are based on all unplanned incidents for subjects at that level of training.

[a] $P < 0.03$ versus experienced.

[b] $P < 0.05$ CA1 versus experienced, average number of unplanned incidents per simulated case.

[c] $P < 0.05$ CA1 versus CA2, distribution of error types.

[d] $P < 0.05$ versus experienced.

performance of anesthesia personnel at different levels of training when faced with the same case management situations. Although there are many caveats concerning interpretation of the data and about the use of this simulation technique (2), these studies provide a unique window of the changes in problem-handling ability that occur with education and experience in anesthesiology.

Not surprisingly, there was a detectable difference between novice residents and more experienced trainees, faculty, and practitioners. There was a trend toward earlier detection and correction of the planned critical incident as the level of experience increased. The detection time decreased with experience for all events except for the IV line occlusion. Likewise, the latency time decreased with experience for the occluded IV line, atrial fibrillation, and airway disconnection. There was no change in latency time for the endobronchial intubation and ventricular tachycardia. Statistical analysis of these trends was made difficult by the heterogeneity of variances between groups. Nevertheless, this heterogeneity may itself be important, supporting the hypothesis that there are some characteristics of problem solving that are different between the groups studied. There was no apparent systematic difference between faculty and private practitioners (Figure 1), although no statistical analysis of this hypothesis was possible. The faculty and practitioners were all highly experienced, and it is possible that fully trained anesthesiologists with less practice experience would have performed differently. This hypothesis could not be tested in our experiment.

The variances in response times were large within the experienced group for all planned events, and for each individual there was a difference in detection and correction times between the different planned events. This high intraindividual variance in performance has been noted in our trainee studies (2,3) and in previous studies of medical problem solving (7–11). It has been attributed to differences in problem-solving strategy or to the level of difficulty of different medical problems. In our study, the planned events were purposely chosen to cover different levels of difficulty. The difficulty (as we perceived it) did not always correspond to the time needed for correction, as illustrated by the kinked IV line event, which was intended to be simple for experienced anesthesiologists but in fact took them a long time to detect.

The behavior of outliers may provide the best insight into mechanisms of human error during anesthesia. The maximal correction time for each of the incidents was due to a different subject, and nearly all subjects made at least one error. One experienced anesthesiologist had 12 unplanned incidents, whereas the average was five unplanned incidents per case and one individual had no unplanned incidents. It is possible that some individuals consistently respond more rapidly and with fewer errors than others, either because of intrinsic differences in personality or because of acute differences in performance-shaping factors such as fatigue or stress. However, this experiment was not designed to test such an hypothesis.

Problem Solving in Medicine

To interpret the findings of this study, we looked toward existing models of problem solving in medicine. Traditional thinking about medical problem solving viewed the physician as formally generating and testing specific hypotheses (12–14). In our analysis of both spontaneous "thinking aloud" and focused probing during debriefing, we were unable to confirm that the subjects' actions were the result of testing specific hypotheses. This traditional hypothesis-testing view of medical diagnosis has been challenged by a view that emphasizes the diagnostician's structured knowledge base as a guide to optimal diagnostic inquiry (14). However, we did not see optimized and formal inquiry either. Rather, we mostly observed "pattern matching" based on the perceived highest frequency explanation for one or more findings, often triggered by only a single abnormality. This is an example of the "frequency gambling heuristic" described by Reason (15); similar phenomena have been observed in internal medicine trainees (16).

The dynamic nature of anesthesia may necessitate such heuristics. We have previously described (17,18) the adaptation to anesthesiology of models of problem solving developed for other complex worlds such as process control or nuclear power (19–21). Although our observations do not prove the validity of these models for anesthesiologists, they do provide hints of the actual cognitive processes involved. We are just beginning to investigate the nature of anesthesia expertise, and it will take carefully structured studies to delineate the precise boundaries of the anesthesiologist's cognitive abilities.

The most fundamental component of the dynamic models is Rasmussen's categorization of human behavior into skill-based, rule-based, and knowledge-based performance (21,22). Briefly, skill-based behavior represents sensorimotor activities that take place without conscious control—smooth, automated, and highly integrated patterns of behavior. Vascular cannulation and endotracheal intubation are such activities. Rule-based behavior relies on precompiled subroutines in a familiar work situation, subroutines that may have been derived during previous occasions. Much of intraoperative management appears to occur at this level. Finally, knowledge-based behavior is seen in situations unfamiliar to the operator for which no rules are available, when rule-based responses have not succeeded, and also in the selection and modification of rules as required. Preoperative evaluation may involve causal reasoning at this level. We added (18) a fourth "supervisory control" level in which attention is allocated between the other levels and between different tasks or problems.

During administration of an anesthetic, knowledge-based behavior provides the anesthesiologist with a means of generating solutions based on causal pathophysiologic reasoning as well as generating solutions to novel problems. This behavior corresponds most closely to the traditional model of hypothesis generation and testing. Its high probability of ultimate success (if the knowledge base is adequate) comes at the expense of efficiency and speed. Experience provides the ability to use rule-based behavior as a shortcut to the problem solution, with a confidence that may approach the knowledge-based solution but at greater speed and efficiency. In general, the expert, but not the novice, can be expected to act both accurately and quickly and to be able to alter standard operating procedure to meet unusual needs. Pattern-matching for a particular event should occur more often with experienced individuals because novices would be less likely to have already formulated appropriate mental patterns. Furthermore, even when the novice recognizes a pattern, the responses to it are likely to be poorly formed routines that have not been optimized, or modified for the situation at hand. Thus, the heterogeneity of variances between the groups could be due to the novice's reliance on undifferentiated reasoning whereas experts were relying on reliable shortcuts based on experience.

At the supervisory control level, the experienced anesthesiologist should be more likely to allocate attention preferentially to the most critical factors, yielding faster correction of problems and the ability to handle more tasks simultaneously. On the other hand, the experienced subjects in our study may have allocated so much attention to the airway and the cardiopulmonary system that they were delayed in detecting the simple but important IV line occlusion.

Assuming that there is truly a difference between the novice's dependence on an undifferentiated knowledge base and on the use of poorly formed rules and responses to the expert's efficient rule-based reasoning, when might the change occur? The mean time-response data in our study suggest that the transition may occur sometime between the CA1 and CA2 years. The heterogeneity of the variances indicates that this transition occurs at different times for different problems, but in all cases sometime during the residency years. Liu and Mitchell (23) demonstrated that the knowledge-based learning behavior of anesthesia residents changes during residency from one focused on the acquisition of large amounts of detailed information through memorization to one focused on conceptualization. Presumably this is mirrored by the progressive integration of rule-based clinical response routines.

Ubiquity of Human Error

Although the anesthesiologists' responses to planned incidents, on average, improved with experience, the failure of individuals in each group to correctly solve certain planned problems, and the occurrence of unplanned incidents, reinforces the concept that human error is ubiquitous in anesthesia regardless of experience. Although fewer errors were made by experienced individuals, they made the same type of errors as did the novices. The errors covered the spectrum of failure modes previously described (18) and involved different failures at each of the cognitive levels. Like Rasmussen (21), we have emphasized that human error cannot be completely prevented and have suggested strategies aimed at making errors more observable and strengthening the preparation and training of the anesthesiologist to handle whatever events arise (24). Based on these initial simulation studies we believe that the development of an adjunct curriculum (25) to focus on problem-solving strategies in anesthesia might help trainees and practitioners to optimize their responses to critical incidents. The CASE 1.2 simulator was originally designed as a research tool, but we are convinced that simulators like it will be used to enhance the skills anesthetists require to avert anesthetic mishaps.

The authors thank George Yang and Thomas Lee for technical assistance and Susan Ryan, PhD, for review of the manuscript.

References

1. Cooper JB, Newbower RS, Kitz RJ. An analysis of major errors and equipment failures in anesthesia management: considerations for prevention and detection. Anesthesiology 1984;60:34–42.
2. Gaba DM, DeAnda A. The response of anesthesia trainees to simulated critical incidents. Anesth Analg 1989;68:444–51.
3. DeAnda A, Gaba DM. Unplanned incidents during comprehensive anesthesia simulation. Anesth Analg 1990;71:77–82.
4. Gaba DM, DeAnda A. A comprehensive anesthesia simulation environment: re-creating the operating room for research and training. Anesthesiology 1988;69:387–94.
5. Cooper JB, Newbower RS, Long CD, McPeek B. Preventable anesthesia mishaps: a study of human factors. Anesthesiology 1978;49:399–406.
6. Sokol RR, Rohlf FJ. Biometry. San Francisco: WH Freeman, 1981:744–5.
7. Marshall J. Assessment of problem-solving ability. Med Educ 1977;11:329–34.
8. McGuire CH, Babbott D. Simulation techniques in the measurement of problem-solving skills. J Educ Measure 1967;4:1–10.
9. Normal GR, Tugwell R, Feightner JW. A comparison of resident performance on real and simulated patients. J Med Educ 1982;57:708–15.
10. Levine H, McGuire CH. The validity and reliability of oral examinations in assessing cognitive skills. J Educ Measure 1970;7:63–74.
11. Fielding DW, Page GG. Development and validation of written simulation problems for pharmacy. Am J Pharm Educ 1978;42:270–80.
12. Barrows HS, Tamblyn RS. Problem based learning: an approach to medical education. New York: Springer, 1980:19–56.
13. McGuire CH. Medical problem-solving: a critique of the literature. J Med Educ 1985;60:587–95.
14. Groen GJ, Patel VL. Medical problem-solving: some questionable assumptions. Med Educ 1985;19:95–100.
15. Reason J. Modelling the basic error tendencies of human operators. Reliability Eng System Safety 1988;20:137–53.
16. Elstein AS, Shulman LS, Sprafka SS. Medical problem-solving: an analysis of clinical reasoning. Cambridge, Mass.: Harvard University Press, 1978:64–121.
17. Gaba DM, Maxwell M, DeAnda A. Anesthetic mishaps: breaking the chain of accident evolution. Anesthesiology 1987;66:670–6.
18. Gaba DM. Human error in anesthetic mishaps. Int Anesthesiol Clin 1989;27:137–47.
19. Woods DD. Coping with complexity: the psychology of human behavior in complex systems. In: Goodstein LP, Anderson HB, Olsen SE, eds. Tasks, errors, and mental models. London: Taylor & Francis, 1988:1282-48.
20. Reason J. Generic error-modeling system (GEMS): a cognitive framework for locating common human error forms. In: Rasmussen J, Duncan K, Leplat J, eds. New technology and human error. Chichester, U.K.: Wiley, 1987;63–83.
21. Rasmussen J. Information processing and human-machine interaction: an approach to cognitive engineering. New York: Elsevier, 1986:100–5.
22. Rasmussen J. Cognitive control and human error mechanisms. In: Rasmussen J, Duncan K, Leplat J, eds. New technology and human error. Chichester, U.K.: J. Wiley 1987:53–61.
23. Liu PL, Mitchell R. Learning behavior differences between CA1 and CA3 residents (abstract). Anesthesiology 1989;71:A970.
24. Cooper JB, Gaba DM. A strategy for preventing anesthesia accidents. Int Anesthesiol Clin 1989;27:148–52.
25. Gott SP. Technical intuition in system diagnosis, or accessing the libraries of the mind (abstract). Aviat Space Environ Med 1988;59:A59–A64.

Comparison of Kinetics of Sevoflurane and Isoflurane in Humans

Nobuhiko Yasuda, MD, PhD, Stephen H. Lockhart, PhD, MD, Edmond I. Eger II, MD, Richard B. Weiskopf, MD, Jin Liu, MD, Michael Laster, DVM, Shahram Taheri, BS, and Natalie A. Peterson, BS

YASUDA N, LOCKHART SH, EGER EI II, WEISKOPF RB, LIU J, LASTER M, TAHERI S, PETERSON NA. Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 1991;72:316–24.

The low solubility of sevoflurane in blood suggests that this agent should enter and leave the body more rapidly than isoflurane. However, the closeness of sevoflurane and isoflurane tissue/blood partition coefficients suggests that the rates of equilibration with and elimination from tissues should be similar. We tested both predictions, comparing sevoflurane with isoflurane and nitrous oxide in seven volunteers. We measured the rate at which the alveolar (end-tidal) (FA) concentration of nitrous oxide increased toward an inspired (FI) concentration of 65%–70%, then measured the concurrent rise in FA and mixed expired concentrations (FM) of sevoflurane and isoflurane at respective FI values of 1.0% sevoflurane and 0.6% isoflurane for 30 min. Minute ventilation ($\dot{V}$E) was measured concurrently with the measurements of anesthetic concentrations. For the potent agents, we also measured $\dot{V}$E, FA, and FM for 6–7 days of elimination. FA/FI values at 30 min of administration were as follows: nitrous oxide, 0.986 ± 0.003 (mean ± SD); sevoflurane, 0.850 ± 0.018; and isoflurane, 0.733 ± 0.027. FA/FA$_0$ (FA$_0$ = the last FA during administration) values after 5 min of elimination were as follows: sevoflurane, 0.157 ± 0.020; isoflurane, 0.223 ± 0.024. Recovery (volume of anesthetic recovered during elimination/volume taken up) of sevoflurane (101% ± 7%) equaled recovery of isoflurane (101% ± 6%). Time constants for a five-compartment mammillary model for sevoflurane were smaller than those for isoflurane for the lungs but were not different from isoflurane for the other compartments. In summary, we found (a) that FA/FI of sevoflurane increases and FA/FA$_0$ decreases more rapidly than do these variables with isoflurane in humans; but (b) that elimination from tissues did not differ between sevoflurane and isoflurane; and (c) that the metabolism of sevoflurane did not differ from that estimated for isoflurane.

Key Words: ANESTHETICS, VOLATILE—sevoflurane, isoflurane. ANESTHETICS, GASES—nitrous oxide. PHARMACOKINETICS, SEVOFLURANE, ISOFLURANE.

The blood/gas partition coefficient of sevoflurane is smaller than that of isoflurane (1), indicating a more rapid increase in FA/FI and more rapid decrease in FA/FA$_0$ with sevoflurane, where FA is the alveolar (end-tidal) concentration, FI is the inspired concentration, and FA$_0$ is the last FA during administration. This prediction is supported qualitatively by the results of a study of sevoflurane in dogs (2). However, the difference in kinetics of isoflurane and sevoflurane may be overestimated by comparing blood solubilities because the tissue/blood partition coefficients of sevoflurane are greater than those of isoflurane (3). Studies of fluoride serum levels and excretion in human volunteers indicate that sevoflurane is metabolized (4) and thereby suggest that metabolism may accelerate elimination as it does for halothane (5).

Although these findings suggest that the rate of change of FA/FI and FA/FA$_0$ will be more rapid with sevoflurane, no data directly compare the kinetics for these two anesthetics in humans. Existing data also suggest that studies of mass balance should reveal smaller recovery of sevoflurane than of isoflurane. However, a preliminary study of the pharmacokinetic characteristics of these agents in swine failed to show less recovery of sevoflurane (6).

To define better the relative metabolism and rates of change of FA/FI and FA/FA$_0$ for sevoflurane and isoflurane in humans, we measured these variables

---

Support for this study was supplied in part from Maruishi Pharmaceutical and the Anesthesia Research Foundation.

Received from the Departments of Anesthesia and Physiology, and the Cardiovascular Research Institute, University of California, San Francisco, California, and the Department of Anesthesiology, the Jikei University School of Medicine, Tokyo, Japan. Accepted for publication October 16, 1990.

Address correspondence to Dr. Eger, Department of Anesthesia, Room S-455, Box 0464, University of California, San Francisco, CA 94143-0464.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

during the concurrent administration and elimination of the anesthetics. We conducted a mass balance study to determine whether the increased levels of fluoride in plasma and urine after anesthesia with sevoflurane reflect a metabolism that alters uptake and elimination. We compared the FA/FI and FA/FA_0 for sevoflurane with those for nitrous oxide (N_2O), an anesthetic having a lower blood/gas partition coefficient (7). Finally, we compared the FA/FI and FA/FA_0 for sevoflurane with those variables for desflurane and halothane. Data for the last two agents were taken from a parallel study (8).

Materials and Methods

With approval from the University of California, San Francisco Committee on Human Research and informed consent from subjects, we studied seven healthy male volunteers (age 23 ± 3 yr [mean ± SD], body weight 72 ± 9 kg, height 182 ± 7 cm). An 18-gauge intravenous catheter was placed, and lactated Ringer's solution was infused at 100–150 mL/h. Anesthesia was induced by intravenous injection of 0.1–0.2 mg/kg midazolam and 2–5 μg/kg fentanyl. After oxygenation via mask, 10 mg vecuronium was administered intravenously to facilitate endotracheal intubation. Ventilation was controlled via a nonrebreathing system to produce normocapnea (end-tidal carbon dioxide [CO_2] of 5.5%–6.5%), and, thereafter, 70% N_2O was administered for 30 min with inspired and end-tidal concentrations of N_2O and CO_2 measured by mass spectrometry and recorded. After the 30 min of administration of N_2O, basal anesthesia was maintained with 65% N_2O supplemented by intravenous administration of midazolam and fentanyl, as indicated by blood pressure and heart rate. Blood pressure and heart rate were measured noninvasively by an oscillometric method (Dinamap, Criticon Co./Johnson & Johnson). Paralysis was maintained by intravenous administration of vecuronium guided by the response to train-of-four electrical stimulation by the ulnar nerve. Esophageal temperature was monitored and maintained at 35.6°–36.9°C using a Bair Hugger (Augustine Medical Inc.) forced air warmer.

Cylinders containing 1.0% sevoflurane and 0.6% isoflurane, balance 35% oxygen and 65% N_2O, were prepared. Soon after the 30-min period of N_2O administration, a square-wave of this mixture was administered for 30 min via a nonrebreathing circuit. The expiratory limb of the circuit was composed of corrugated Teflon tubing connected to a 1-L aluminum mixing chamber (to mix alveolar and dead space gases and thereby supply a mixed expired sample). The output from the mixing chamber was connected to a spirometer. Ports permitted sampling of end-tidal (FA), mixed expired (FM), and inspired (FI) gas. To define the pharmacokinetics of the potent agents during their administration, end-tidal samples were collected from the first five breaths and then from breaths at 0.75, 1, 1.5, 2, 3, 5, 7.5, 10, 12.5, 15, 20, 25, and 29 min. Minute ventilation ($\dot{V}E$) was measured, and mixed expired and inspired samples were collected at 5, 7.5, 10, 12.5, 15, 20, 25, and 29 min.

Precisely at 30 min, administration of the volatile anesthetics was discontinued and the breathing circuit was exchanged with a fresh inspiratory and expiratory circuit. A basal level of anesthesia was continued with 65% N_2O, midazolam, fentanyl, and vecuronium. For the measurement of elimination of the potent agents, end-tidal samples were collected from the first five breaths, then from breaths at 0.75, 1, 1.5, 2, 3, 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 210, 240, 300, 400, 500, 600, 800, and 1400 min, and on each morning thereafter for 6–7 days. Ventilation and mixed expired and inspired samples were measured at 5, 7.5, 10, 12.5, 15, 20, 25, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 210, 240, 300, 400, 500, 600, 800, and 1400 min, and on each morning thereafter for 6–7 days. After 150 min of elimination, the administration of the basal anesthesia was discontinued and the elimination of N_2O was measured. This measurement was taken for 10 min or shorter if the subject coughed or moved. The endotracheal tube was then removed. Thereafter, gas samples were collected through a mouthpiece and a nonrebreathing valve connected by Teflon tubing to a mixing chamber (as described earlier) and a spirometer. Nose clips were used to prevent breathing through the nose. All gas samples were taken in 50-mL glass syringes sealed with nylon three-way stopcocks. The syringes were stored upright until the gas contents were analyzed.

All samples were analyzed for concentration of the volatile anesthetics by gas chromatography. We used two Gow-Mac series 580 flame ionization detector gas chromatographs, each equipped with a 6-m-long stainless steel column (3 mm in diameter) packed with Chromosorb-WHT 60–80 mesh maintained at 48°C. One had a nitrogen carrier stream flowing at 5–6 mL/min delivered through the column to a flame ionization detector at 150°C, supplied by hydrogen at 12–15 mL/min and by air at 200 mL/min, equipped with a 0.1-mL sample loop for high concentrations. The other was equipped with a 1.0-mL sample loop for lower concentrations and had a nitrogen carrier stream flowing at 22–24 mL/min delivered through the column to a flame ionization detector at 200°C, supplied by hydrogen at 15–17 mL/min and by air at 200 mL/min. Results were recorded on a strip-chart recorder. The chromatographs were calibrated with secondary tank standards that had been calibrated with primary standards produced by injection of a liquid aliquot of anesthetic by micropipette into a flask of known volume. Peak heights were proportional to concentration over the entire range of concentrations studied, and linearity of the gas chromatographs was confirmed over the range of concentrations measured.

We used the values for FM, FA, and FI obtained at 10, 15, and 20 min to provide an estimate for FM during the first 3 min using the formula

$$F_M = f_A \times F_A + f_D \times F_I,$$

where fA equals the fraction of ventilation coming from the alveoli and fD equals the fraction of ventilation coming from the dead space. The average values for fA and fD calculated from the 10-, 15-, and 20-min samples were obtained using this same formula (i.e., substitute 1 − fA for fD to solve for fA; and substitute 1 − fD for fA and solve for fD). Then, using the measured values of FA and FI for the first 3 min, we calculated FM for this time period.

The ratio of FA to FI (FA/FI) was used to define the pharmacokinetics during anesthetic administration. The ratio of FA to FA_0 (FA/FA_0) was used to define anesthetic elimination. FA_0 is the alveolar concentration of anesthetic found immediately before discontinuing administration of sevoflurane and isoflurane. The FA/FI and FA/FA_0 at each time point were compared among the anesthetics using a paired t-test with a Bonferroni correction for multiple comparison when needed (9).

Multiexponential (multicompartment) models of the form

$$\sum_{i=0}^{n} A_i e^{-\lambda_i t}$$

were fit to the elimination data using least-squares (hybrid) analysis (10,11). We will refer to this analysis as the "hybrid" analysis to distinguish it from a second analysis (see below) that we will refer to as the "mammillary"analysis. A_i has no units. λ_i has units of reciprocal time (min^{-1}); and t is time (min). We fit equations (models) having successively more exponents (interpreted as compartments) to the data for each anesthetic for each subject (i.e., for each of the 14 data sets that we obtained—from the two potent agents given to seven subjects). For each data set, the model having the greatest number of compartments (highest n) that significantly decreased the residual sum of squares when compared with the model having one less compartment ($n-1$) was considered to provide the "best fit" ($P < 0.05$, F-ratio test) (12).

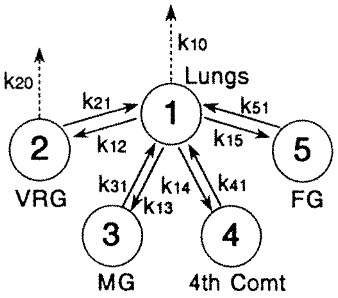


Figure 1. The five-compartment model used in determining the mammillary constants (k_{21-51} and k_{12-15}) is represented schematically. Compartments 1–5 represent the central compartment, the vessel-rich group (VRG), the muscle group (MG), the fourth compartment, and the fat group (FG), respectively. k_{10} and k_{20} represent pulmonary elimination and hepatic metabolism, respectively.

Hybrid time constants were calculated from the rate constants (λ_i) as $1/\lambda_i$ for each compartment. The time constants for five-compartment models for the two potent agents were compared, and the significance of any difference assessed using paired t-tests.

We also calculated rate constants for these data using a five-compartment mammillary model (Figure 1). This model was fit simultaneously to the logarithm of the concentration of anesthetics (sevoflurane and isoflurane) in end-tidal gas (FA) and the logarithm of the rate of excretion of the anesthetics via the lungs for each subject by using five differential equations to describe the rate of change in anesthetic concentration in each compartment. A method involving the matrix exponential was used to integrate effectively the differential equations (13). Fitting the excretion data simultaneously enabled us to estimate the mammillary rate constant for the metabolism of the anesthetics in the second compartment (interpreted as the vessel-rich group, containing the liver). These data analyses yielded estimates of the volume of the central compartment (V_1) and mammillary rate constants: the elimination rate constants k_{10} and k_{20}, and the intercompartmental transfer rate constants k_{1j} and k_{j1} (where $j = 2, \ldots, 5$) (Figure 1). Elimination of anesthetics was permitted from two sites: the central compartment (lungs; k_{10}) and the second compartment (vessel-rich group; k_{20}). These sites were chosen because volatile anesthetics are eliminated from the body primarily by exhalation and by metabolism (via the liver). From the mammillary rate constants, we calculated transit times $[1/(k_{10} + k_{12} +$

$k_{13} + k_{14} + k_{15}$), $1/(k_{20} + k_{21})$, and $1/k_{j1}$ (where $j = 3, 4, 5$)]. Transit times for $1/k_{j1}$ also equal the time constants for respective compartments. Time constants for the central compartment ($1/k_{10}$), vessel-rich group ($1/k_{21}$), and hepatic elimination from the vessel-rich group ($1/k_{20}$) also were calculated.

Assuming that the delivery of anesthetic to the tissues is perfusion- and not diffusion-limited, the mammillary rate constants may be used to estimate blood flow and tissue volume (14). To do so requires knowing the anesthetic's tissue/blood and tissue/gas partition coefficients for the particular tissue group. For this analysis, we assumed that the second, third, and fifth compartments were the vessel-rich, muscle, and fat tissues, respectively. We assumed that the fourth compartment also was fat. To estimate flow (mL perfusion·100 mL tissue^{-1}·min^{-1}) for any tissue group (e.g., the jth tissue group), we multiplied the tissue/blood partition coefficient (which we determined previously) (3), by the corresponding calculated mammillary rate constant value [i.e., k_{j1} (where $j = 2, \ldots, 5$)] and by 100. To calculate the volume for each tissue, we multiplied the estimate of the volume of the central compartment by the ratio of the mean mammillary rate constants [i.e., k_{1j}/k_{j1} (where $j = 3, 4, 5$) and $k_{12}/(k_{10} + k_{21})$ for the vessel-rich tissues] obtained for the periods of administration and elimination and divided the resulting number by the tissue/gas partition coefficient (3). Using regression analysis (15), we also compared the volumes obtained for fat (the volumes for the fourth compartment plus the volume for the fat group) with fat volumes obtained by the measurement of skinfold thickness (16). The measurement from the skinfold thickness gave an estimate of the percentage of body weight that fat comprised. This percentage was converted to volume by multiplying by body weight and by 0.92 (assumed to equal the specific gravity of fat). We used the fat volumes derived from the skinfold measurements and from mammillary analysis for isoflurane from this and a parallel study (8). The incorporation of the data from the parallel study increased the number of subjects to 11. In addition to the regression comparing fat volumes derived from these two approaches, we also correlated fat volumes obtained from skinfold measurements with the fat group mammillary time constant.

For each subject, total body clearances for both potent agents were calculated by dividing the doses of each anesthetic delivered to the alveoli (calculated as $F_I \times \dot{V}_A \times 30$ min, where $\dot{V}_A$ equals $f_A \times \dot{V}_E$) by the areas under the alveolar administration and elimination curves. We estimated the area under the alveolar anesthetic concentrations against time by the trapezoidal rule. The area under the elimination curve from the last data point to time infinity was calculated by taking the ratio of the last alveolar anesthetic concentration and the estimate of the terminal hybrid rate constant. These data were tested by paired t-tests for differences in total body clearance between sevoflurane and isoflurane.

We assessed the total pulmonary uptake and elimination of sevoflurane and isoflurane as follows: uptake and elimination rates were calculated for each anesthetic at each time point. Uptake rates were calculated as $\dot{V}_E \times (F_I - F_M)$. Elimination rates were calculated as $\dot{V}_E \times F_M$. Total uptake for each anesthetic was estimated as the area under the curve generated by plotting the anesthetic uptake rate against time (trapezoidal method). Total recovery of unchanged anesthetic in exhaled gases (i.e., elimination by ventilation) (mass balance) was calculated by the same method, and terminal recovery was estimated by multiplying the elimination rate at the final time point by the terminal hybrid time constant (determined separately for each anesthetic in each subject, as described earlier). Percent recovery (i.e., the percentage of anesthetic taken up that is eliminated by ventilation) of each anesthetic was calculated as the total recovery divided by the total uptake and multiplied by 100.

These mass balance data were then used to determine the extent of anesthetic metabolism. We assumed that isoflurane was not metabolized but that the percentage recovery of isoflurane might differ from 100% because of other sources of anesthetic loss (e.g., through the skin and in the urine), or because of inconsistencies in ventilation and circulation (e.g., our measurements always were taken with volunteers at or near basal state; however, after release from the hospital [after 1440 min], subjects pursued normal activities, probably exceeding basal levels for at least a fraction of each day and potentially influencing measurements taken on days 2–7 after their release). We also assumed that other sources of anesthetic loss or inconsistencies in ventilation or circulation would affect the recovery of each anesthetic proportionately. To compensate for these losses, not only did we calculate the absolute percent recovery of each anesthetic but also the percent recovery of sevoflurane normalized to that of isoflurane (the latter, by dividing the percent recovery of sevoflurane by the percentage recovery of isoflurane). Deficits in percent recovery were assumed to be due to metabolism. Differences between sevoflurane and isoflurane were analyzed by paired t-test. We accepted $P < 0.05$ as significant for all measurements.

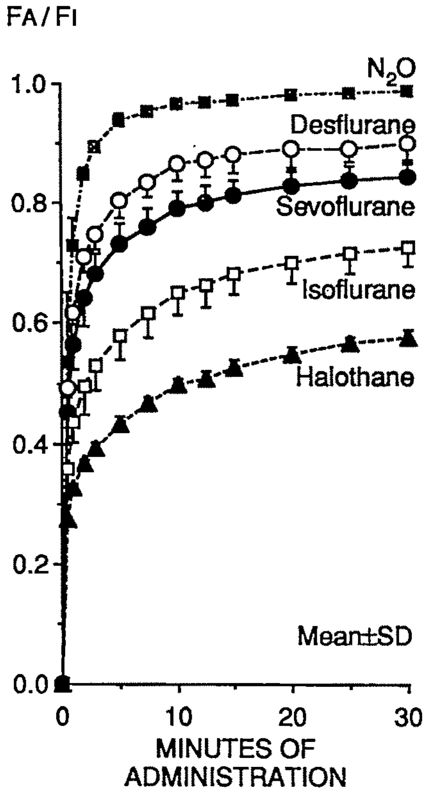


Figure 2. The pharmacokinetics of sevoflurane and isoflurane during their administration are defined as the ratio of end-tidal anesthetic concentration (FA) to inspired anesthetic concentration FI (i.e., FA/FI) (mean ± SD). Consistent with its relative blood/gas partition coefficient, the FA/FI of sevoflurane increases more rapidly than that of isoflurane or halothane but slower than that of N_2O or desflurane.

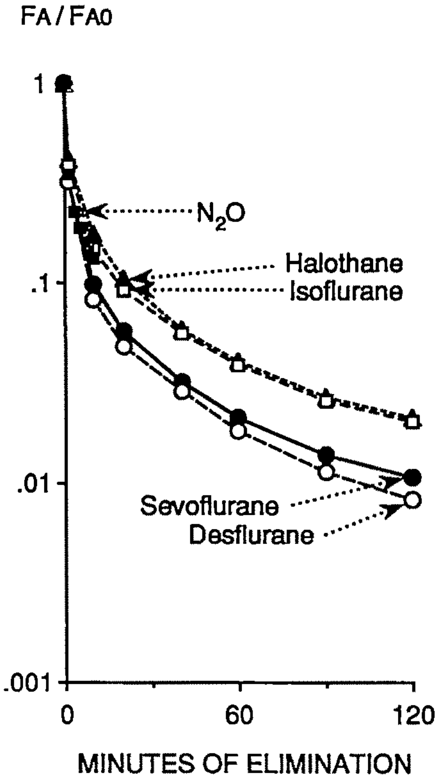


Figure 3. Elimination of each anesthetic is defined as the ratio of end-tidal anesthetic concentration (FA) to the FA immediately before the beginning of elimination (FA_0) (i.e., FA/FA_0). Over the 120-min period portrayed, the elimination of sevoflurane is faster than that of isoflurane by a factor of about 1.6 (note the logarithmic scale for the ordinate). The elimination rate of sevoflurane is slightly slower than that of desflurane, whereas the elimination rates of isoflurane and halothane are indistinguishable. Elimination of N_2O is slower (n only equals 2) than with sevoflurane because equilibration with N_2O was 8 to 10 times longer.

Results

In addition to results for pharmacokinetics from this study, results from a similar study investigating desflurane, isoflurane, and halothane (8) are shown in Figures 2–4. The differences between these two studies were reconciled by normalizing the desflurane and halothane data for each individual to the isoflurane data in the present study (i.e., normalized data = [desflurane or halothane data] × [present isoflurane data]/[other isoflurane data]).

FA/FI of sevoflurane increased and FA/FA_0 decreased more rapidly than did these variables for isoflurane and halothane (Figures 2–4). FA/FI of sevoflurane increased more slowly than did this variable for desflurane and N_2O. Elimination of sevoflurane was slower than that for desflurane but faster than that for N_2O.

All 14 data sets of elimination fit best to a five-compartment model. Applying the suggestion of Carpenter et al. (5), we interpreted the first, second, third, fourth, and fifth compartments as representing the lungs, vessel-rich group (VRG), muscle group (MG), a layer of fat that receives anesthetic from adjacent vessel-rich organs by intertissue diffusion (fourth compartment), and fat group (FG), respectively. Values for A_1 were larger for sevoflurane, whereas values for A_2 through A_5 were larger for isoflurane (Table 1). Relative to isoflurane, sevoflurane hybrid time constants for VRG were smaller; did not differ for the MG, fourth compartment, and FG; and were larger for the lungs (Table 2). Although statistically significant, the differences between sevoflurane and isoflurane values for the VRG and lungs were too small to be of clinical importance.

The volume of the central compartment (V_1) of sevoflurane (2.10 ± 0.62 L) was smaller than that of isoflurane (2.31 ± 0.71 L). The mammillary elimination rate constant from the central compartment (k_{10}) for sevoflurane was greater than that for isoflurane (Table 3). Pulmonary elimination clearances, defined as (V_1) times (k_{10}), were not different between sevoflurane (3.58 ± 0.43 L/min) and isoflurane (3.62 ±

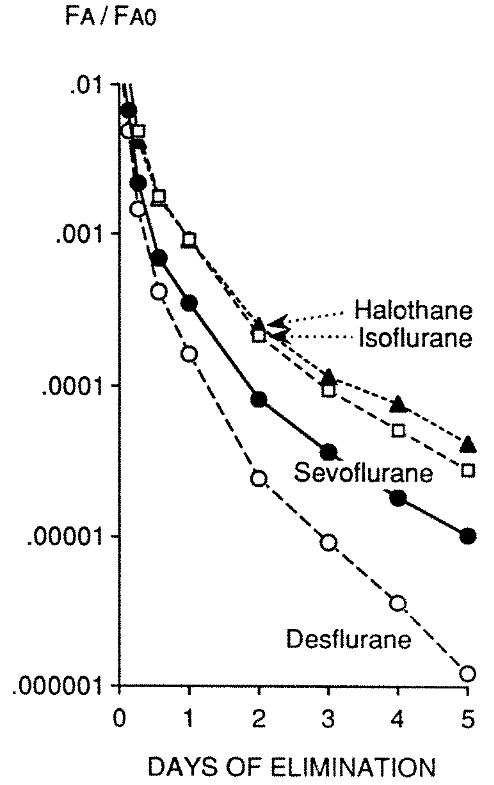


Figure 4. The terminal elimination of sevoflurane is faster than that of isoflurane but is slower than that of desflurane. After 2–5 days, there is a two- to threefold difference between the values for sevoflurane and isoflurane. The difference between the values for desflurane and sevoflurane progressively increase after day 1 and approach eightfold by day 5.

Table 1. A_i Coefficients ×100

Coefficient	Compartment	Sevoflurane	Isoflurane
A_1	Lungs	63.6 ± 2.9[a]	55.7 ± 3.1
A_2	Vessel-rich group	24.7 ± 3.5[a]	26.9 ± 4.0
A_3	Muscle group	4.60 ± 3.14[a]	7.19 ± 4.04
A_4	Fourth compartment	0.717 ± 0.800[a]	1.296 ± 1.237
A_5	Fat group	0.028 ± 0.018[a]	0.072 ± 0.044

Values are expressed as mean ± SD.

[a] Significantly different from isoflurane ($P < 0.05$).

Table 2. Hybrid Washout Time Constants (min)

Compartment	Sevoflurane	Isoflurane
Lungs	0.46 ± 0.08[a]	0.39 ± 0.09
Vessel-rich group	9.17 ± 4.08[a]	9.80 ± 4.31
Muscle group	81.7 ± 42.6	85.0 ± 42.1
Fourth compartment	437 ± 163	474 ± 162
Fat group	2230 ± 730	2310 ± 930

Values are expressed as mean ± SD.

[a] Significantly different from isoflurane ($P < 0.05$).

Table 3. Mammillary Rate Constants (min^{-1})

Rate constant	Sevoflurane	Isoflurane
k_{10}	1.78 ± 0.32[a]	1.64 ± 0.33
k_{12}	0.709 ± 0.145[a]	1.26 ± 0.204
k_{13}	0.223 ± 0.035[a]	0.402 ± 0.055
k_{14}	0.125 ± 0.056[a]	0.243 ± 0.072
k_{15}	0.0310 ± 0.0196[a]	0.0646 ± 0.0414
k_{21}	0.194 ± 0.092	0.210 ± 0.082
k_{31}	0.0231 ± 0.0198	0.0230 ± 0.0156
k_{41}	0.00313 ± 0.00180	0.00304 ± 0.00169
k_{51}	0.000502 ± 0.000117	0.000500 ± 0.000119
k_{20}	0.0094 ± 0.0171	0.0093 ± 0.0137

Values are expressed as mean ± SD.

[a] Significantly different from isoflurane ($P < 0.05$).

Table 4. Mammillary Time Constants and Transit Times (min)

Time constant or transit time	Sevoflurane	Isoflurane
$1/k_{10}$ (lungs)	0.580 ± 0.120[a]	0.634 ± 0.143
$1/(k_{10} + k_{12} + k_{13} + k_{14} + k_{15})$	0.355 ± 0.055[a]	0.281 ± 0.037
$1/k_{21}$ (vessel-rich group)	6.17 ± 2.65	5.38 ± 1.94
$1/(k_{20} + k_{21})$	6.05 ± 2.72	5.20 ± 1.93
$1/k_{31}$ (muscle group)	63.3 ± 31.6	57.0 ± 26.0
$1/k_{41}$ (fourth compartment)	377 ± 123	383 ± 119
$1/k_{51}$ (fat group)	2,120 ± 690	2,130 ± 680
$1/k_{20}$	5,710,000 ± 5,350,000	4,290,000 ± 5,350,000

Values are expressed as mean ± SD.

[a] Significantly different from isoflurane ($P < 0.05$).

0.41 L/min). Mammillary rate constants from the central compartment to the VRG (k_{12}), MG (k_{13}), fourth compartment (k_{14}), and FG (k_{15}) for sevoflurane were smaller than those for isoflurane. Sevoflurane mammillary rate constants from the peripheral compartments to the central compartment did not differ from those for isoflurane.

Sevoflurane mammillary time constants were smaller than those for isoflurane for the lungs ($1/k_{10}$), but did not differ from isoflurane for the other compartments (Table 4). Mammillary elimination time constants from the VRG ($1/k_{20}$) did not differ between these anesthetics according to nonparametric statistical testing.

With two minor exceptions, neither the calculated blood flows nor the tissue volumes for a given compartment for sevoflurane differed from those for isoflurane (Table 5). The data for sevoflurane gave a slightly greater estimate of blood flow to the FG than the data for isoflurane. The fourth compartment tissue volume for the isoflurane data was greater than

Table 5. Estimated Blood Flow and Tissue Volume

	Blood flow (mL·100 mL tissue^{-1}·min^{-1})		Tissue volume (L)	
Compartment	Sevoflurane	Isoflurane	Sevoflurane	Isoflurane
Vessel-rich group	31 ± 15	31 ± 12	7.4 ± 2.6	7.1 ± 2.5
Muscle group	7.2 ± 6.2	6.7 ± 4.6	11.4 ± 4.8	11.3 ± 5.6
Fourth compartment	15 ± 9	14 ± 8	2.5 ± 0.6[a]	3.0 ± 0.7
Fat group	2.4 ± 0.6[a]	2.2 ± 0.5	4.1 ± 3.0	5.1 ± 4.1

Values are expressed as mean ± SD.
[a]Significantly different from isoflurane ($P < 0.05$).

Table 6. Pulmonary Recovery of Anesthetics

Anesthetic	Total uptake (mL)	Pulmonary elimination (mL)	Anesthetic recovered (%)	Normalized recovery[a] (%)
Sevoflurane	235 ± 45	236 ± 45	101 ± 7	100 ± 4
Isoflurane	236 ± 31	239 ± 37	101 ± 6	100

Values are expressed as mean ± SD.
[a]Normalized to the recovery of isoflurane.

that for the sevoflurane data. Total body clearances of sevoflurane (3.6 ± 0.6 L/min) and isoflurane (3.6 ± 0.5 L/min) did not differ from each other.

The correlation between fat volume estimated from the mammillary rate constants and fat volume defined by skinfold thickness measurements was significant ($r^2 = 0.35$; $P < 0.05$). Similarly, the correlation between mammillary time constants of the FG ($1/k_{51}$) and fat volume estimated by skinfold thickness reached significance ($r^2 = 0.44$; $P < 0.02$).

The recovery of sevoflurane and isoflurane did not differ from each other either as absolute or normalized values (Table 6). The absolute data did not differ from 100%.

Discussion

Relative to sevoflurane, FA/FI increased more rapidly with N_2O and desflurane and less rapidly with isoflurane and halothane (Figure 2). Such results agree with what would be predicted from the relative blood/gas partition coefficients of these anesthetics. They suggest that induction of anesthesia with desflurane and sevoflurane may be more rapid than induction with isoflurane if pungency does not limit the rate at which the inspired concentration of desflurane and sevoflurane may be increased. Similarly, induction with desflurane may be more rapid than induction with sevoflurane. However, clinical experience suggests that induction will be most rapid with sevoflurane because of the greater pungency of desflurane.

FA/FA$_0$ for sevoflurane decreased more rapidly than that for isoflurane (Figures 3 and 4). Again, this is consistent with the smaller solubility of sevoflurane in blood (1) and indicates that recovery from anesthesia with sevoflurane will be more rapid than recovery from isoflurane. Although FA/FA$_0$ for desflurane decreased more rapidly than that for sevoflurane during the first 120 min of elimination, the difference is not great. A more rapid recovery from anesthesia with desflurane than sevoflurane has been found in studies in rats, and both agents had a more rapid recovery than isoflurane and halothane (17).

The differences among sevoflurane, isoflurane, and desflurane increase with the passage of time (Figure 4). Although elimination from muscle and fat does not differ between sevoflurane and isoflurane as indicated by the similar hybrid and mammillary time constants for sevoflurane and isoflurane in the VRG, MG, fourth compartment, and FG, desflurane is eliminated from muscle and fat more rapidly than isoflurane (8). These findings reflect the higher tissue/blood partition coefficients of sevoflurane, isoflurane, and halothane relative to desflurane. That is, elimination of sevoflurane from major depots is slower than that for desflurane and at the same rate as that for isoflurane or halothane. Levels, and thus effects, of "trace" concentrations of sevoflurane may be greater than those of desflurane but less than those of halothane or isoflurane.

We did not show metabolism of sevoflurane by either mass balance or clearance analysis for the VRG (i.e., there was no difference between the values for k_{20}). However, in a similar study using mass balance Carpenter et al. found 10% metabolism of enflurane (18). This metabolism results in an increase in serum inorganic fluoride concentration similar to that produced by sevoflurane (4). Carpenter et al. did not provide a mammillary analysis.

In contrast to their relationship during anesthetic administration, sevoflurane elimination is more rapid than that of N_2O (Figure 2). More rapid elimination of N_2O might have been predicted from the blood/gas partition coefficients for these two agents. Indeed, the elimination of N_2O found by other investigators (19–21) is more rapid than that we found for sevoflurane. The slower elimination of N_2O in our study results from its longer time of equilibration (180 min for N_2O vs 30 min for sevoflurane) and, consequently, greater stores of N_2O in tissues.

Although the elimination of sevoflurane will be more rapid than that of other, presently available, potent agents (and recovery will be more rapid), two properties of sevoflurane suggest that recovery from anesthesia will be less rapid than that achieved with N_2O. First, sevoflurane is more potent and may be used to achieve deeper levels of anesthesia. The larger deposition of anesthetic that results will tend to delay recovery (5). Second, the tissue/blood partition coefficients for sevoflurane (3) are greater than those for N_2O (22–24) and this will proportionately delay clearance of sevoflurane from the tissues, including the brain.

The reader may ask why we undertook both the hybrid and mammillary analyses. We reply that although the analyses overlap in some of the answers they provide, each supplies some unique insights. The mammillary analysis provides the rate constants and (as noted), with a knowledge of partition coefficients, allows estimates of tissue volumes, blood flows, and metabolism. The volumes and flows may be compared with known volumes and flows for the presumed tissue groups to support the presumptions regarding assignment of compartments to specific tissue groups. The hybrid analysis also has some appreciable advantages. It is easier to perform and more robust. Although not a problem in the present study, where we previously were unable to obtain convergence with the mammillary analysis we often succeeded in obtaining convergence using the hybrid analysis. The hybrid analysis provides an economical approach (appreciably less computer time) to defining the least number of compartments best representing the data. It provides an accurate assessment of the terminal time constant used for extrapolation to infinity. It allows a comparison with historical data [e.g., our results for the hybrid time constants for isoflurane are similar to those from the studies by Carpenter et al. (18)] (Table 2).

Moreover, the time constants obtained with hybrid analysis reasonably approximate those obtained by mammillary analysis. This is particularly true of the terminal constants but also applies to the other constants, with the possible exception of the time constant for the first compartment, where mammillary values are approximately twice the hybrid values. In fact, there is an obvious, very high correlation between the hybrid and mammillary results across compartments (i.e., regressing results for all compartments). More impressive yet is the agreement for regressions for within-compartment analyses: the correlation coefficients squared (r^2) range from 0.79 to 0.97 with an average value of 0.87 ± 0.09, except for the lungs where the r^2 value is 0.14. Such data suggest that for these analyses the hybrid results might substitute for or verify the accuracy of the mammillary results.

However, the accuracy and correlation depend on a substantial separation of compartment characteristics. For the present data, the separations are considerable. Each time constant is approximately one order of magnitude greater than the preceding time constant. Where such separation is not achieved, accuracy suffers and the hybrid values may not approximate the mammillary values. Of course, under these circumstances it may be difficult or impossible to determine the mammillary values.

We found a correlation ($r^2 = 0.44$) between the mammillary time constant of the FG and the fat volume in the body estimated by skinfold thickness. This indicates a slower elimination of anesthetics from fat in obese than in lean individuals. Thus, patients with more body fat will be exposed longer to "trace" concentrations than patients with less body fat. This is intuitively obvious. However, it should be noted that only one of our subjects had more than 25% body weight as fat and that excluding the data for this subject resulted in no significant correlation for the remaining subjects whose fat content ranged from 13% to 22%.

The mammillary analysis providing estimations of tissue volumes gave results that were too small for all groups compared with known values (25). Similarly, correlation between fat volume estimated from the mammillary analysis versus skinfold thickness was less than perfect. The result is that our analysis only accounts for about 25 L of the body volume. Even assuming that certain tissues (e.g., cartilage) do not contribute to the uptake process and therefore are "invisible," our analysis clearly produces an underestimate of tissue volumes. The explanation for this discrepancy is not certain.

Similarly, compared to known values (25), our blood flow estimates were too small for the VRG and too large for the MG. Possibly the intertissue diffusion that we believe provides the explanation for the fourth compartment may apply more broadly. Thus the flow (delivery of anesthetic) to the MG may be "enlarged" by its proximity to the VRG.

Indeed, the discrepancy between the predicted and observed values for time constants and tissue volumes calls into question the adequacy of (a) the data, (b) the kinetic analysis, and/or (c) the paradigm presently used to explain pharmacokinetics in physiologic terms. The data may be suspect in that there is an underlying assumption that the end-tidal concentrations accurately indicate the anesthetic partial pressures in arterial blood. Although there appears to be a good correlation between the two, gradients exist (26,27). These will be larger during periods of considerable change in concentration (i.e., during the periods of initial administration and elimination), and thus may confound our ability to accurately predict volumes and time constants for the lungs and VRG. Because the estimates for V_1 also depend to a great extent on the measurements made during this time, V_1 values also may be inaccurately assessed, thereby contributing to erroneous estimates, particularly of tissue volumes. The period after anesthesia when subjects did not remain at a basal state (with consequent changes in ventilation, cardiac output, and distribution of blood flow) also may contribute to discontinuities in the data and hence "errors" in the kinetic analysis. However, this should most affect values for fat, and our calculated values for blood flow appear to accurately reflect known values.

Pulmonary clearances did not differ between sevoflurane and isoflurane despite the twofold differences in their solubilities. Although k_{10} was, as might be anticipated, inversely correlated with solubility, the opposite change in V_1 resulted in the absence of a difference. Similarly, total body clearance of sevoflurane was the same as that of isoflurane. This result would not be predicted from the differences in solubility and biodegradation of these compounds. Both of these factors would favor a more rapid clearance of sevoflurane.

We gratefully acknowledge Alison J. Boeckmann, MS, for her assistance leading to the definition of the mammillary constants, and Winifred von Ehrenburg, MA, for her editorial assistance. We thank Jashvant Unadkat, PhD, for his advice concerning the kinetic analyses. We would like to thank Augustine Medical, Inc., for donating the Bair Hugger forced air warmer.

References

1. Strum DP, Eger EI II. Partition coefficients of desflurane in human blood, saline, and olive oil. Anesth Analg 1987;66: 971–3.
2. Kazama T, Ikeda K. Comparison of MAC and the rate of rise of alveolar concentration of sevoflurane with halothane and isoflurane in the dog. Anesthesiology 1988;68:435–7.
3. Yasuda N, Targ AG, Eger EI II. Solubility of desflurane, sevoflurane, isoflurane, and halothane in human tissues. Anesth Analg 1989;69:370–4.
4. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. Anesthesiology 1981;54:100–6.
5. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Pharmacokinetics of inhaled anesthetics in humans: measurements during and after simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. Anesth Analg 1986;65:575–82.
6. Yasuda N, Eger EI II, Targ AG, Weiskopf RB, Johnson BH. Pharmacokinetics of I-653, sevoflurane, isoflurane, and halothane in swine. Anesth Analg 1990;71:340–8.
7. Siebeck R. Über die Aufnahme von Stickoxydul in Blut. Skand Arch Physiol 1909;21:368–82.
8. Yasuda N, Lockhart S, Eger EI II, Weiskopf RB, Johnson BH, Fassoulaki A. Desflurane, isoflurane, and halothane pharmacokinetics in humans (abstract). Anesth Analg 1990;70:S444.
9. Glantz SA. Primer of biostatistics. New York: McGraw-Hill, 1981:87–8.
10. Jennrich R. Nonlinear regression. In: Dixon WJ, ed. BMDP statistical software. Berkeley: University of California Press, 1983:290–304.
11. Ralston M. Derivative-free nonlinear regression. In: Dixon WJ, ed. BMDP statistical software. Berkeley: University of California Press, 1983:305–14.
12. Boxenbaum HG, Riegelman S, Elashoff RM. Statistical estimations in pharmacokinetics. J Pharmacokinet Biopharm 1974;2: 123–48.
13. Beal SL, Sheiner LB. NONMEM users guide IV. San Francisco: Regents of the University of California, 1984:55.
14. Rowland M, Benet LZ, Graham GG. Clearance concepts in pharmacokinetics. J Pharmacokinet Biopharm 1973;1:123–36.
15. Glantz SA. Primer of biostatistics. New York: McGraw-Hill, 1981:196–211.
16. Durnin JV, Rahaman MM. The assessment of the amount of fat in the human body from measurements of skinfold thicknesses. Br J Nutr 1967;21:681–9.
17. Eger EI II, Johnson BH. Rates of awakening from anesthesia with desflurane, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. Anesth Analg 1987;66:977–82.
18. Carpenter RL, Eger EI II, Johnson BH, Unadkat JD, Sheiner LB. Does the duration of anesthetic administration affect the pharmacokinetics or metabolism of inhaled anesthetics in humans? Anesth Analg 1986;65:575–82.
19. Frumin MJ, Salanitre E, Rackow H. Excretion of nitrous oxide in anesthetized man. J Appl Physiol 1961;16:720–2.
20. Salanitre E, Rackow H, Greene LT, Klonymus D, Epstein RM. Uptake and excretion of subanesthetic concentrations of nitrous oxide in man. Anesthesiology 1962;23:814–22.
21. Sheffer L, Steffenson JL, Birch AA. Nitrous oxide-induced diffusion in hypoxia in patients breathing spontaneously. Anesthesiology 1972;37:436–9.
22. Eger EI II, Larson CP. Anaesthetic solubility in blood and tissues: values and significance. Br J Anaesth 1962;36:140–9.
23. Assali NS, Ross M. Nitrous oxide solubility in fetal and uterine tissues in human pregnancy. Proc Soc Exp Biol 1959;100:497–8.
24. Steward A, Allot PR, Cowles AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil and biological media. Br J Anaesth 1973;45:282–93.
25. Eger EI II. Anesthetic uptake and action. Baltimore: Williams & Wilkins, 1974:88.
26. Eger EI II, Babad AA, Regan MH, Larson CP Jr, Shargel R, Severinghaus JW. Delayed approach of arterial to alveolar nitrous oxide partial pressure in dog and man. Anesthesiology 1966;27:288–97.
27. Carpenter RL, Eger EI II. Alveolar-to-arterial-to-venous anesthetic partial pressure differences in humans. Anesthesiology 1989;70:630–5.

Low-Dose Clonidine Enhances Pregnancy-Induced Analgesia to Visceral but Not Somatic Stimuli in Rats

Hiroshi Iwasaki, MD, PhD, J. G. Collins, PhD, Yoji Saito, MD, Hiroshi Uchida, MD, and Ann Kerman-Hinds, BS

IWASAKI H, COLLINS JG, SAITO Y, UCHIDA H, KERMAN-HINDS A. Low-dose clonidine enhances pregnancy-induced analgesia to visceral but not somatic stimuli in rats. Anesth Analg 1991;72:325–9.

This is one of a series of experiments designed to examine the possible pharmacologic basis for analgesia normally associated with pregnancy. The antinociceptive effects of low-dose (0.1 mg/kg) subcutaneous clonidine on analgesia associated with pregnancy were evaluated in rats. Colorectal distention thresholds and tail-flick latencies were determined in timed pregnant rats (n = 27) before mating, on days 7 and 21 of gestation, and on postpartum day 7. Immediately after baseline testing on each of those days, animals received 0.1 mg/kg clonidine subcutaneously and were retested 30 min later. On day 21 of gestation, 20 μg/kg naloxone (n = 9) and 0.2 mg/kg yohimbine (n = 5) were intravenously administered after clonidine testing, and animals were retested 15 min later.

In the absence of clonidine, pregnant animals demonstrated a statistically significant increase in their tolerance of colorectal distention pressures and longer latencies to tail-flick withdrawal on day 21 of gestation. Clonidine produced a further significant increase in distention thresholds on day 21 of gestation but did not change these thresholds on any other day, nor did it change tail-flick latencies. Naloxone and yohimbine reversed the effect of clonidine on the distention thresholds on day 21.

Systemic clonidine, at a dose lower than that required to produce antinociception in nonpregnant rats, enhanced pregnancy-induced analgesia to visceral stimulation late in pregnancy, an effect that was reversed by naloxone and yohimbine. These results suggest a synergistic antinociceptive effect of clonidine due to an interaction with an endogenous opiate system that is only activated late in pregnancy.

Key Words: PREGNANCY, PHYSIOLOGIC ANALGESIA. ANESTHESIA, OBSTETRICAL—pregnancy-induced analgesia.

There is a general clinical impression that a parturient has a lowered requirement for anesthetics and analgesics. A possible explanation for these observations is that endogenous analgesic mechanisms are stimulated by pregnancy, resulting in a phenomenon that has been referred to as "pregnancy-induced analgesia." A recent study has provided evidence that pregnancy increases median nerve susceptibility to lidocaine in humans (1), and both human and animal studies have reported a pregnancy-induced analgesia (2,3). In the human study (2), pressure-induced pain thresholds were observed to increase during the last 16 days of pregnancy. In the rat study (3), pain thresholds were observed to rise abruptly during the last 2 days of the 21-day gestation period. Not all reports, however, support the existence of analgesia normally associated with pregnancy (4,5). Because of the difficulty in producing a reliable, noninvasive, repeatable visceral stimulus, previous studies typically have not evaluated visceral pain in pregnant animals even though visceral pain is of obvious importance to the management of labor pain. We have recently demonstrated the adequacy of colorectal distention as a visceral stimulus for use in pregnant rats and have also confirmed the existence in rats of a pregnancy-induced, naloxone-reversible analgesia to both somatic and visceral stimuli late in pregnancy and the early postpartum period (6).

Clonidine, an α_2-adrenergic receptor agonist, widely used as a clinical antihypertensive drug, is an agent of considerable interest to anesthetists because of its antinociceptive properties both in experimental animals (7–10) and in humans (11,12). Of particular interest to

---

Presented in part at the meeting of the International Anesthesia Research Society, Honolulu, Hawaii, March 1990.

Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication October 30, 1990.

Address correspondence to Dr. Collins, Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

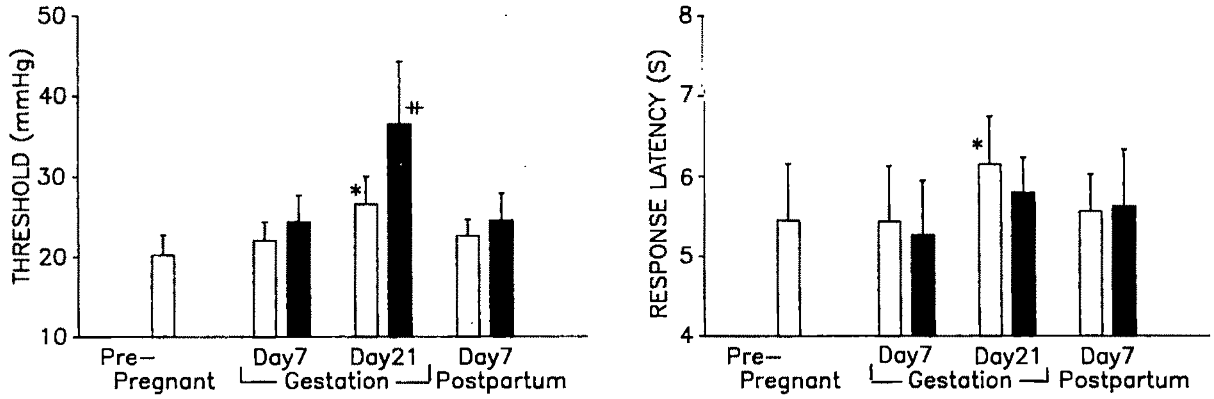


Figure 1. Comparison of colorectal distention thresholds (*left*) and tail-flick latencies (*right*) before (*open bars*) and after (*filled bars*) subcutaneous administration of 0.1 mg/kg clonidine in pregnant rats. A statistically significant increase in thresholds for colorectal distention ($n = 27$) and tail-flick latencies ($n = 11$) on day 21 of gestation was demonstrated. Colorectal distention thresholds after clonidine administration on day 7 of gestation and postpartum day 7 were not significantly different from preclonidine values. On day 21 of gestation, there was a significant increase in colorectal distention thresholds compared with preclonidine values. Clonidine produced no significant changes in tail-flick latencies. *$P < 0.05$ compared with prepregnant baseline values. ╫ $P < 0.05$ compared with preclonidine values on day 21 of gestation. *Vertical bars* indicate mean ± SD.

the study reported here is the fact that an enhancement of opiate analgesia after the administration of clonidine by several different routes has been reported (13–16). Clinically, the combination of a small dose of morphine and clonidine provides a new approach to reduce morphine requirements and to delay the onset of morphine tolerance in terminally ill patients in pain (17,18).

Because pregnancy-induced analgesia is naloxone-reversible and small doses of clonidine have been shown to powerfully enhance opiate analgesia, we hypothesized that low doses of clonidine would increase pregnancy-induced analgesia to both somatic and visceral noxious stimulation. The purpose of this study was to test that hypothesis. This study was previously reported in abstract form (19).

Materials and Methods

This protocol was approved by the Yale University Animal Care and Use Committee. A total of 31 female Sprague–Dawley rats, weighing 250–300 g at the start of the experiments, were used. Animals were housed in individual cages, with free access to food and water, and were kept on a 12-h light/dark cycle with lights on at 6 AM.

Rats were time-mated, and the first day on which mucous plugs were detected in the cage was designated as day 1 of pregnancy. To reduce the effects of handling on nociceptive responses, all animals were handled and trained in the test situation for at least 3 days before testing, and all measurements were made by the same experimenter.

Two tests (colorectal distention, tail-flick) were used to assess each animal's response to noxious visceral and somatic stimuli. The colorectal distention apparatus and methods were modified from Ness and Gebhart (20), who demonstrated the aversive nature of the stimulus including cardiovascular and visceromotor changes suggestive of noxious stimulation. Colorectal distention involves inflation with air of a 7–8-cm-long, pressure-monitored, flexible latex balloon introduced into the descending colon and rectum. The balloon is inserted through the anus under light halothane anesthesia, but animals are awake during testing. Intracolonic pressure is continuously monitored via an in-line pressure transducer. Air pressure within the intracolonic balloon is steadily increased at a rate of 2 mm Hg/s beginning at 0 mm Hg until contraction of abdominal musculature is detected by sudden increases in recorded pressure that are associated with palpable constriction of abdominal musculature. The pressure at which abdominal constrictions are triggered by balloon distention is defined as the threshold response of colorectal distention. To prevent tissue damage, a cut-off distention pressure of 60 mm Hg is employed.

Standardized tail-flick testing was employed by monitoring latency to withdrawal from a heat source (a 50-W projection lamp bulb) focused on a distal segment of the tail (approximately 2 cm from the tip). The location on the tail that was stimulated was systematically varied so that the same portion of the tail was not exposed repeatedly to the light source. A 10-s cut-off point was employed in the tail-flick tests to minimize tissue damage.

After determining baseline colorectal distention thresholds and tail-flick withdrawal latencies, animals ($n = 27$) were mated and retested at days 7 and 21 of gestation and 7 days after parturition. Immediately after testing on those days, animals were given 0.1 mg/kg clonidine subcutaneously (doses based on weight on day 7 of gestation) and then retested at 30 min, a time of peak effect as revealed in time-course studies. In addition, in 12 of 27 pregnant rats, either 20 μg/kg naloxone ($n = 7$) or 0.2 mg/kg yohimbine ($n = 5$) (doses based on weight on day 21 of gestation) was administered intravenously on day 21 of gestation 20 min after the administration of clonidine, and animals were retested 15 min later. Doses of naloxone and yohimbine were determined in a separate pilot study. Clonidine and yohimbine were dissolved in normal saline and administered in a volume of 1.0 mL/kg.

Each colorectal distention and tail-flick test was repeated six times at each time-point with a 30-s intertrial interval. The mean of the last three tests at each test time-point was used for analysis. Values are presented as the mean ± SD. Statistical comparisons of mean thresholds and withdrawal latencies were performed with analysis of variance and Student's *t*-tests. Differences were considered to be statistically significant at $P < 0.05$.

Results

Baseline colorectal distention values (20.3 ± 2.44 mm Hg) were similar to those reported by Ness and Gebhart to be aversive in nonpregnant awake rats (20). As shown in Figure 1, pregnant animals demonstrated a statistically significant increase in thresholds for colorectal distention and latencies to tail-flick withdrawal on day 21 of gestation. Colorectal distention thresholds after subcutaneous administration of 0.1 mg/kg clonidine on day 7 of gestation and postpartum day 7 were not significantly different from preclonidine values. In contrast, on day 21 of gestation, clonidine administered at a dose of 0.1 mg/kg produced a significant increase in colorectal distention thresholds (36.5 ± 7.65 mm Hg) compared with preclonidine values on day 21 (26.7 ± 3.31 mm Hg). The mean body weights of animals on days 7 and 21 of gestation and postpartum day 7 were 317.7 ± 40.7 g, 420.8 ± 49.2 g, and 324.0 ± 37.7 g, respectively. The mean dose of clonidine that pregnant animals received on day 21 of gestation when based on their weight on day 7 of gestation was 0.08 ± 0.006 mg/kg. As shown in Figure 1, clonidine produced no significant change in tail-flick latencies throughout the study.

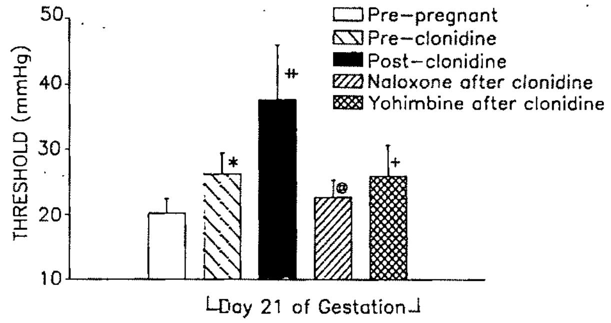


Figure 2. Effects of intravenous administration of either 20 μg/kg naloxone or 0.2 mg/kg yohimbine on colorectal distention thresholds on day 21 of gestation after the subcutaneous administration of 0.1 mg/kg clonidine in pregnant rats. On day 21 of gestation, significantly elevated thresholds after clonidine administration were significantly antagonized by naloxone ($n = 9$) to prepregnant baseline values and by yohimbine ($n = 4$) to preclonidine values. $^{*}P < 0.05$ compared with prepregnant baseline values. ⧺ $P < 0.05$ compared with preclonidine values on day 21. $^{@}P < 0.05$ compared with clonidine values on day 21. $^{+}P < 0.05$ compared with clonidine values on day 21. *Vertical bars* indicate mean ± SD.

The change in distention thresholds was apparent at 10 min (34.2 ± 7.82 mm Hg), with a peak effect at 30 min (38.7 ± 6.56 mm Hg), and persisted for approximately 1 h after clonidine administration.

The potentiating effect of 0.1 mg/kg clonidine as assessed by colorectal distention on day 21 of gestation was antagonized to prepregnant baseline values by 20 μg/kg naloxone ($n = 5$) administered intravenously and was also reversed by 0.2 mg/kg yohimbine ($n = 4$) administered intravenously (Figure 2).

Discussion

As we have previously confirmed (6), pregnancy-induced analgesia to visceral and somatic noxious stimulation is evident late in pregnancy in rats. Additionally, systemic clonidine, at a lower dose than that required to produce significant antinociception, enhanced the pregnancy-induced analgesia to noxious visceral stimulation late in pregnancy.

The possible role of α_2-adrenergic receptors in antinociception has been suggested by the fact that clonidine when administered alone by several routes in a number of animal models (7–10) as well as in humans (11,12) produces a potent antinociceptive effect. Clonidine also potentiates the antinociceptive effect of morphine, the administration of combinations of clonidine and morphine producing a synergistically greater analgesia than that produced by either drug alone but avoiding the side effects of both agents, including the development of tolerance to morphine or clonidine (13–16). The analgesic effect of clonidine has been believed to act mainly through an opiate-independent mechanism because the effect is antagonized by the α_2-adrenergic antagonist yohimbine but not the opiate antagonist naloxone (21–23). However, a naloxone-reversible component of the analgesic effect of clonidine has been recently observed in rats (24).

The present study showed that the potentiating effect of a low dose of clonidine observed only on day 21 of gestation was completely antagonized by naloxone to prepregnant baseline values and was also reversed by the α-adrenergic antagonist yohimbine to preclonidine values. These observations strongly suggest that the synergistic antinociceptive effect of low-dose clonidine is produced by an interaction with an endogenous opiate system that is only active near the time of parturition (no similar effect was seen on day 7 of gestation and postpartum day 7).

Interestingly, the present results demonstrated that the small dose of clonidine produced no significant change in tail-flick tests at any test time-point. Clonidine has been shown to be effective in increasing the latency of tail-flick responses as well as decreasing the number of writhes induced by injection of irritating chemical solutions in nonpregnant animal studies (25,26). Intrathecal clonidine has also been shown to dose-dependently inhibit responses to colorectal distention (27). The absence of a clonidine effect on tail-flick latencies in this study suggests that at low dose there may be a selective antinociceptive effect on visceral stimuli. There is evidence for quantitatively different effects of clonidine and morphine on visceral and cutaneous spinal nociceptive transmission (28). An alternative explanation is that because the stimuli were not of equivalent intensity, the drug effect appears to be selective for colorectal distention.

Selectivity for visceral stimuli has been associated with κ-opiate receptors because it has been reported that κ-agonists exert a selective suppression of response on visceral chemical writhing tests but are less active at inhibiting a cutaneous thermal evoked reflex (29). A recent report has indicated that the κ-opiate receptor subtype is involved in modulating the analgesia of pregnancy in rats (30). These results raise the possibility that the selective effect of low-dose clonidine administered systemically on visceral stimuli in this study is due to an α-adrenergic–κ-opiate interaction.

Although our interpretation of the data is that the threshold of a noxious stimulus has been elevated, we must also consider the possibility that clonidine, by influencing the autonomic nervous system, changed the smooth muscle response to distention. Such a change may not be associated with noxious information but would still be of interest because it was only observed on day 21 of gestation.

Because a major part of pain sensation in labor is associated with visceral nociception from uterine, cervical, and peritoneal fibers, the synergistic interaction that we observed in this study may prove to be clinically useful in the design of control strategies for labor pain. The complex nature of sensory processing within the spinal dorsal horn provides many opportunities to modulate noxious afferent input. By better understanding the systems responsible for that modulation, we may be able to amplify the body's own ability to regulate pain sensation.

In conclusion, a naloxone-reversible analgesia to visceral and somatic stimulation was demonstrated late in pregnancy in rats. Low-dose clonidine produced marked behavioral effects on visceral but not somatic stimuli late in pregnancy in rats. The present results provide additional confirmation of previous reports that the terminal stages of pregnancy and the early postpartum period in rats are associated with elevated pain thresholds that are opioid-mediated.

References

1. Butterworth JF, Walker FO, Lysak SZ. Pregnancy increases median nerve susceptibility to lidocaine. Anesthesiology 1990; 72:962–5.
2. Cogan R, Spinnato JA. Pain and discomfort thresholds in late pregnancy. Pain 1986;27:63–8.
3. Gintzler AR. Endorphine-mediated increases in pain threshold during pregnancy. Science 1980;210:193–5.
4. Dunbar AH, Price DD, Newton RA. An assessment of pain responses to thermal stimuli during stages of pregnancy. Pain 1988;35:265–9.
5. Dahl JL, Silva BW, Baker TB, Tiffany ST. Endogenous analgesia in the pregnant rat: an artifact of weight-dependent measures? Brain Res 1986;373:316–23.
6. Iwasaki H, Collins JG, Saito Y. Pregnancy-induced naloxone reversible analgesia (abstract). Anesth Analg 1989;68:S131.
7. Reddy SVR, Yaksh TL. Spinal noradrenergic terminal system mediates antinociception. Brain Res 1980;189:391–401.
8. Bloor BC, Flacke WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist. Anesth Analg 1982;61:741–5.
9. Eisenach JC, Dewan DM, Rose JC, Angelo JM. Epidural clonidine produces antinociception, but not hypotension, in sheep. Anesthesiology 1987;66:496–501.
10. Ossipov MH, Chatterjee TK, Gebhart GF. Locus coerleus lesions in the rat enhance the antinociceptive potency of centrally administered clonidine but not morphine. Brain Res 1985;341:320–30.
11. Boico O, Bonnet F, Rostaing S, Loriferne JF, Quintin L, Ghingcne M. Epidural clonidine produces postoperative analgesia. Anesthesiology 1988;69:A388.
12. Coombs DW, Saunders RL, Fratkin JD, Jensen LE, Murphy CA. Continuous intrathecal hydromorphone and clonidine for intractable cancer pain. J Neurosurg 1986;64:890–4.

13. Yaksh TL, Reddy SVR. Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. Anesthesiology 1981;54:451–67.
14. Drasner K, Fields HL. Synergy between the antinociceptive effects of intrathecal clonidine and systemic morphine in the rat. Pain 1988;32:309–12.
15. Murata K, Nakagawa I, Kumeta Y, Kitahata LM, Collins JG. Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic range neurons in cats. Anesth Analg 1989;69:185–91.
16. Ossipov MH, Suarez LT, Spaulding TC. Antinociceptive interactions between alpha 2-adrenergic and opiate agonists at the spinal level in rodents. Anesth Analg 1989;68:194–200.
17. Gold MS, Pottash AC, Sweeney DR, Kleber HD. Opiate withdrawal using clonidine. A safe, effective and rapid nonopiate treatment. JAMA 1980;243:343–6.
18. Coombs DW, Saunders RL, Lachance D, Savage S, Regnarsson TS, Jensen LE. Intrathecal morphine tolerance: use of intrathecal clonidine, DADLE, and intraventricular morphine. Anesthesiology 1985;62:358–63.
19. Iwasaki H, Collins JG, Saito Y, Uchida H. Low dose clonidine enhances pregnancy induced analgesia to visceral but not somatic stimuli in rats (abstract). Anesth Analg 1990;70:S171.
20. Ness TJ, Gebhart GF. Colorectal distention as a noxious visceral stimulus: physiologic and pharmacologic characterization of pseudaffective reflexes in the rats. Brain Res 1988;450: 153–69.
21. Yaksh TL, Noueihed R. The physiology and pharmacology of spinal opiates. Ann Rev Pharmacol Toxicol 1985;25:433–62.
22. Solomon RE, Gebhart GF. Intrathecal morphine and clonidine: antinociceptive tolerance and cross-tolerance and effects on blood pressure. J Pharmacol Exp Ther 1988;245:444–54.
23. Spaulding T, Fielding S, Venafro JJ, Lal H. Antinociceptive activity of clonidine and its potentiation of morphine analgesia. Eur J Pharmacol 1979;58:19–25.
24. Mastrianni JA, Abbott FV, Kunos G. Activation of central μ-opioid receptors is involved in clonidine analgesia in rats. Brain Res 1989;479:283–9.
25. Bentley GA, Newton SH, Starr J. Studies on the antinociceptive action of alpha-agonist drugs and their interactions with opioid mechanisms. Br J Pharmacol 1983;79:125–34.
26. Browning S, Lawrence D, Livingston A, Morris B. Interactions of drugs active at opiate receptors and drugs active at alpha 2-receptors on various test systems. Br J Pharmacol 1982;77: 487–91.
27. Danzebrink RM, Gebhart GF. Antinociceptive effects of intrathecal adrenoceptor agonists in a rat model of visceral nociception. J Pharmacol Exp Ther 1990;253:698–705.
28. Ness TJ, Gebhart GF. Differential effects of morphine and clonidine on visceral and cutaneous spinal nociceptive transmission in the rat. J Neurophysiol 1989;62:220–30.
29. Schmauss C, Shimohigashi Y, Jensen TS, Rodbard D, Yaksh TL. Studies on spinal opiate receptor pharmacology. III. Analgetic effects of enkephalin dimers as measured by cutaneous-thermal and visceral-chemical evoked responses. Brain Res 1985;337:209–15.
30. Sander HW, Kream RM, Gintzler AR. Spinal dynorphin involvement in the analgesia of pregnancy: effects of intrathecal dynorphine antisera. Eur J Pharmacol 1989;159:205–9.

330 ANESTH ANALG
1991;72:330–6

Multiple-Dose Evaluation of Intravenous Hydromorphone Pharmacokinetics in Normal Human Subjects

Harlan F. Hill, PhD, Barbara A. Coda, MD, Akira Tanaka, DDS, PhD, and Randy Schaffer, MS

HILL HF, CODA BA, TANAKA A, SCHAFFER R. Multiple-dose evaluation of intravenous hydromorphone pharmacokinetics in normal human subjects. Anesth Analg 1991;72:330–6.

We measured the pharmacokinetics of hydromorphone in normal volunteers given three doses of the drug (10, 20, and 40 μg/kg) as intravenous 45-s injections on different days. Concentrations of hydromorphone in plasma from serial blood samples were measured by a high-performance liquid chromatography method specific for hydromorphone with a detection limit of 0.1 ng/mL. In all cases, plasma hydromorphone concentration versus time data for individual subjects were best described by a triexponential (instead of mono- or biexponential) function. Furthermore, we found that the pharmacokinetics of hydromorphone was independent of dose across the range studied. Averaged across doses, the distribution and terminal elimination half-lives were 1.27 min ($t_{1/2\pi}$), 14.7 min ($t_{1/2\alpha}$), and 184 min ($t_{1/2\beta}$), respectively. Average values for systemic clearance, initial dilution volume, and steady-state volume of distribution were 1.66 L/min (Cl), 24.4 L (Vc), and 295 L (Vd_{ss}). Our results indicate that hydromorphone pharmacokinetic parameters are linear across a fourfold range of doses that are usually employed clinically and that previously reported pharmacokinetic values for hydromorphone (based on radioimmunoassay measurements) deserve reconsideration.

Key Words: ANALGESICS, HYDROMORPHONE—pharmacokinetics. PHARMACOKINETICS, HYDROMORPHONE.

Hydromorphone, the 6-oxo derivative of morphine, is an opioid with appreciable selectivity for μ-opioid receptors. Pharmacodynamically, hydromorphone differs from the parent drug mainly in potency. The onset and duration of clinical analgesic effect of hydromorphone and morphine are similar (1,2). Like morphine, hydromorphone is a hydrophilic opioid with an octanol/water partition coefficient of about 1 (3) although even lower values (i.e., 0.3) have been reported (4). Hydromorphone is excreted mainly as the 3-glucuronide in humans (5), and little if any hydromorphone-6-glucuronide is formed in humans.

For a drug that has been used clinically for so many years, it is surprising that the pharmacokinetics of hydromorphone has not been thoroughly studied. In the two pharmacokinetic studies that have been published, radioimmunoassays designed for measurement of morphine were employed without assurances that they were specific for hydromorphone quantitation; theoretically, hydromorphone metabolites could cross-react with the antibody. Vallner et al. (6) measured hydromorphone concentrations in plasma of patients given 2-mg bolus intravenous injections of hydromorphone. They reported that hydromorphone followed "single-compartment" pharmacokinetics, with an elimination half-life of 158 min, apparent (extrapolated) volume of distribution of 91 L, and total clearance of about 0.4 L/min. In the other study (7), hydromorphone pharmacokinetics was best described by biexponential decay curves in normal volunteers. Parab et al. (7) reported distributional and elimination half-lives of 4.2 and 142 min, respectively, total clearance of 1.02 L/min, initial dilution ("central compartment") volume of 16 L, and an apparent volume of distribution of 203 L. As is apparent, the studies differ markedly in most respects and the pharmacokinetics of hydromorphone after intravenous dosing remains unclear. Furthermore, in previous studies, blood was not sampled early enough after the bolus hydromorphone doses to characterize fully the distributional properties of the drug.

Supported by grants from the National Institute on Drug Abuse (DA 05513) and the National Cancer Institute (CA 38552), and by assistance from Abbott Laboratories.

Received from the Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, Washington; and the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington. Accepted for publication October 31, 1990.

Address correspondence to Dr. Hill, Pain and Toxicity Research Program, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Hydromorphone is receiving renewed attention as an alternative to morphine for treatment of prolonged cancer-related pain (8,9). Because it can be prepared in more concentrated aqueous solutions than morphine and because it is about seven times more potent (1,10), hydromorphone is being used with increasing frequency in cancer patients who require high parenteral doses of an opioid analgesic for long-term pain control. This resurgent interest in hydromorphone has increased the importance of improving our understanding of hydromorphone pharmacokinetics in human subjects. In this report, we describe results obtained in a group of relatively young, healthy volunteers as a basis for comparison of hydromorphone pharmacokinetics in cancer patients of both similar and different ages involved in studies in progress.

We used a specific high-performance liquid chromatography method to determine the pharmacokinetics of hydromorphone at three different intravenous dose levels in a group of 10 normal volunteers in order to further define pharmacokinetic parameters of this widely used opioid and to establish whether or not its pharmacokinetics was dose-dependent. This represents the first detailed report on hydromorphone pharmacokinetics using highly specific high-performance liquid chromatography for measuring plasma hydromorphone concentrations in human subjects.

Methods

Subjects

Ten healthy volunteers, men between 21 and 38 yr of age with body weights of 63.4–99.2 kg (mean, 72.7 kg) were recruited for this study. All subjects were within ±10% of norms for body weight and height. All subjects gave informed consent as approved by the Institutional Review Board of Fred Hutchinson Cancer Research Center.

Subject Preparation

On each test day, we placed 22-gauge catheters in the basilic vein of the subject's left arm for drug administration and in the right arm for blood sampling. We drew blood samples into heparinized syringes just before and 1, 2, 3, 4, 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, and 300 min after a 45-s injection of 10, 20, or 40 μg/kg of hydromorphone (calculated as base). Blood samples were placed on ice until the end of each test session and then were centrifuged to obtain plasma samples. Plasma was stored at −40°C for later assay of hydromorphone concentration. A minimum of 7 days separated all hydromorphone doses in each subject. We randomized the order of administration of the three doses within and across subjects.

Hydromorphone Assay

We employed a modification of the general method of Todd et al. (11). For extraction of hydromorphone, 1-mL aliquots of plasma were thoroughly mixed with 1.5 mL sodium borate buffer (pH 8.96) and the internal standard (20 ng nalorphine). Samples were applied to liquid-liquid extraction columns (Chem-Elute CE1003) and allowed to equilibrate for 5 min. We eluted hydromorphone and nalorphine from the columns with two 5-mL portions of chloroform/isopropanol (95:5). We evaporated the organic solvent completely with a stream of nitrogen at 45°C, redissolved the residue in 400 μL mobile phase, and injected 20 μL for chromatographic analysis. Extraction recoveries for hydromorphone from plasma averaged 87% with a 9.1% coefficient of variation.

We performed hydromorphone analyses on a Varian 5060 high-performance liquid chromatograph using an ESA coulometric detector set at +0.75, 0.25, and 0.45 V for guard, cell 1, and cell 2, respectively. A Supelco C18DB column (15 cm × 4.6 mm, 5-μm particle size) and a guard column of the same material were used. The column was heated to 40°C. The mobile phase was 0.07 M phosphate buffer at pH 3.47, methanol, acetonitrile (87:9:4) at a flow rate of 1.0 mL/min. Within-day coefficients of variation at 1, 5, 10, and 20 ng/mL were 6.8%, 6.3%, 4.5%, and 4.0%, respectively, as determined with samples of blank human plasma to which known amounts of hydromorphone and internal standard were added (n = 10–12 samples per concentration). Between-day coefficient of variation at 20 ng/mL was 6.7%. The detection limit for hydromorphone was 0.1 ng/mL (3 × signal/noise).

Data Analysis

Plasma hydromorphone concentration versus time data from each subject at each dose were fit to biexponential and triexponential decay curves by nonlinear least-squares regression with constant weighting of 1/variance, with variance estimated as the predicted concentration squared (12). We chose the best fit in each case based on the lesser sum of

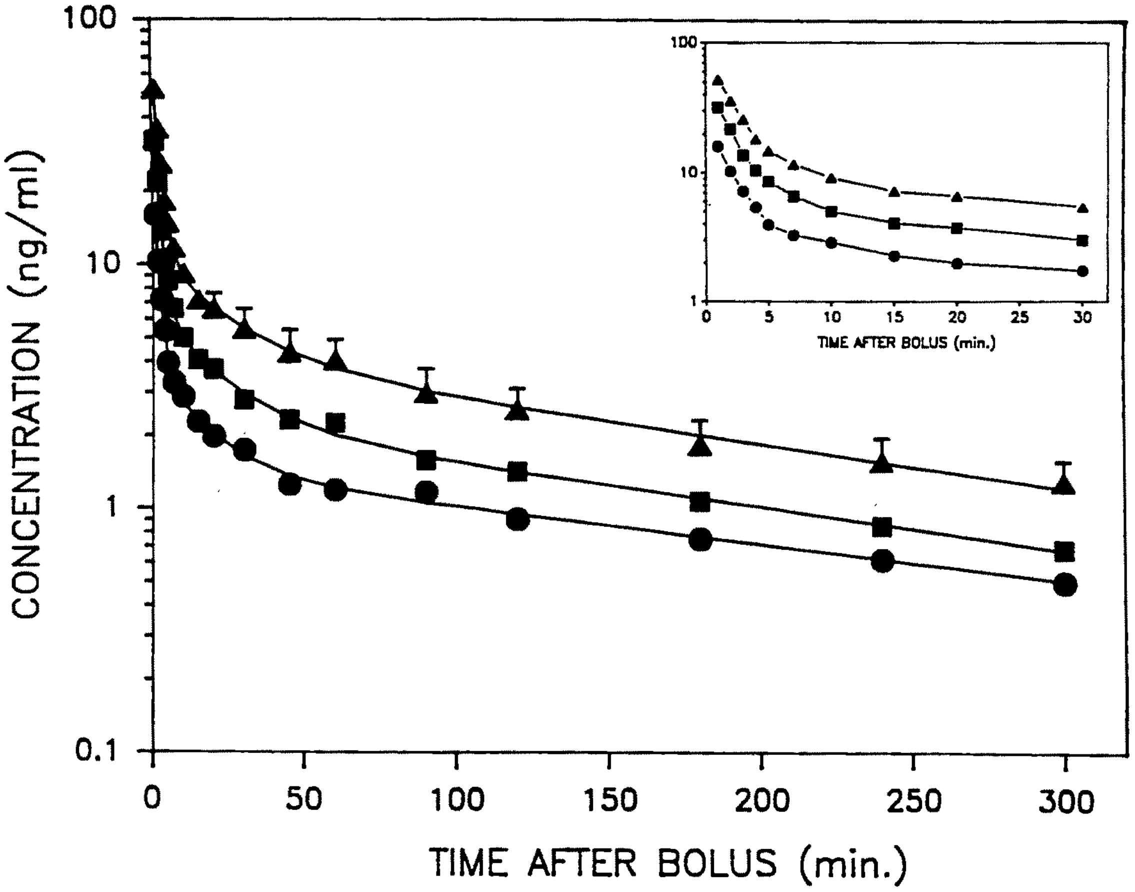


Figure 1. Plasma concentrations of hydromorphone after intravenous bolus doses. Values are mean (±SE) for 10 subjects at each dose. Data points are measured concentrations, and lines represent the nonlinear least-squares fits of the mean concentration-versus-time data at each dose. ●, 10 μg/kg; ■, 20 μg/kg; ▲, 40 μg/kg.

squared residuals with adjustment for the number of exponentials according to Akaike (13). We used individual subject exponential coefficients for $Cp = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$ to calculate distributional half-lives, central compartment volume, and hybrid rate constants; total clearance and steady-state distribution volume were calculated from area under the concentration-time curve (AUC, extrapolated to infinity using the last measured concentration/β) and AUMC, the first moment of AUC (14). Differences across doses in the mean pharmacokinetic parameters were examined by analysis of variance for significance ($P < 0.05$).

Results

The mean measured concentrations ($n = 10$) of hydromorphone at each sampling time are shown in Figure 1. Nonlinear least-squares fits of the mean data for each dose indicated that the hybrid rate constants for net loss of hydromorphone from plasma were very similar across doses for the group of subjects.

All individual concentration-versus-time data sets were best described by triexponential (versus biexponential) equations for each subject and dose according to standard criteria (13). Individual subject values for the constants and exponents of the triexponential decay curves are shown in Table 1. There was a two- to eightfold variation across subjects in values for each coefficient.

The triexponential coefficients, along with AUC and mean residence time (MRT), are shown as group means and standard error in Table 2. The exponential coefficients (P, A, B) as well as AUC were linearly related to dose, as expected. There were no significant differences in the rate constants (π, α, β) or MRT across doses.

Standard pharmacokinetic parameters are displayed in Table 3. Again, we found no significant dose-related differences for any of the parameters. For each pharmacokinetic parameter, individual sub-

Table 1. Triexponential Coefficient Rate Constants for Individual Subjects

	10 μg/kg						20 μg/kg						40 μg/kg					
Dose	P	A	B	π	α	β	P	A	B	π	α	β	P	A	B	π	α	β
1	52.6	3.0	1.2	0.64	0.060	0.0046	51.1	7.7	2.6	0.70	0.068	0.0038	181	22.1	3.4	1.5	0.116	0.0057
2	8.1	2.3	1.2	0.39	0.026	0.0019	52.1	5.8	2.8	1.2	0.109	0.0049	123	12.2	6.8	1.1	0.136	0.0056
3	31.4	1.8	0.9	0.55	0.017	0.0023	56.9	3.2	2.6	0.55	0.033	0.0030	54.7	3.5	5.6	0.48	0.034	0.0050
4	10.9	3.7	1.2	0.35	0.082	0.0071	34.8	6.2	2.3	0.66	0.078	0.0051	48.8	6.7	2.8	0.46	0.021	0.0027
5	20.6	2.7	1.5	0.70	0.090	0.0038	35.9	6.1	1.6	0.57	0.064	0.0035	50.9	3.5	4.4	0.34	0.024	0.0021
6	14.7	1.7	1.0	0.43	0.054	0.0028	52.1	2.6	1.5	0.43	0.050	0.0028	82.1	12.3	4.3	0.59	0.143	0.0050
7	16.4	0.8	1.2	0.47	0.055	0.0121	41.2	6.2	2.9	1.1	0.114	0.0095	45.9	4.6	4.0	0.47	0.067	0.0069
8	10.6	0.8	0.9	0.29	0.025	0.0018	45.8	3.4	1.8	0.43	0.023	0.0023	54.6	7.3	5.0	0.40	0.039	0.0055
9	46.2	1.5	1.8	0.93	0.045	0.0039	34.1	3.6	2.4	0.47	0.054	0.0046	119	10.3	4.5	0.71	0.062	0.0064
10	30.5	2.5	1.6	0.77	0.072	0.0051	101	6.8	3.0	0.79	0.061	0.0042	137	12.9	4.7	0.69	0.068	0.0040
CV%	61	43	23	35	45	55	37	33	22	37	42	44	50	57	23	50	61	30
Range[a]	6.5	4.0	2.0	3.2	5.3	6.3	3.0	2.9	1.8	2.7	4.8	4.1	3.7	6.2	2.4	4.3	6.8	3.3

P, A, and B are exponential coefficients in ng/mL and π, α, and β are hybrid rate constants in min^{-1}. Coefficients of variation (CV% = SD/mean × 100) provide an index for comparison of relative variation in individual values across coefficients and doses.

[a] Range = highest value/lowest value.

Table 2. Analysis of Variance: Coefficients and AUC for Triexponential Fits of Individual Subject Data

	10 μg/kg	20 μg/kg	40 μg/kg	F	P
P	24.21 (4.90)	50.49 (6.19)	89.68 (14.97)	15.40	0.000
A	2.08 (0.30)	5.17 (0.56)	9.53 (1.81)	9.77	0.001
B	1.26 (0.10)	2.35 (0.17)	4.54 (0.35)	51.41	0.000
π	0.552 (0.064)	0.686 (0.083)	0.671 (0.112)	0.26	0.717
α	0.053 (0.009)	0.065 (0.010)	0.070 (0.014)	0.15	0.862
β	0.0045 (0.0010)	0.0044 (0.0006)	0.0049 (0.0005)	0.17	0.845
AUC	500 (72)	757 (68)	1319 (145)	40.80	0.000
MRT	240 (54)	207 (23)	185 (30)	1.40	0.220

AUC is the area under the plasma concentration versus time curve ($\text{ng}\cdot\text{mL}^{-1}\cdot\text{min}^{-1}$), and MRT is mean residence time (min). P, A, and B (ng/mL) and π, α, and β (min^{-1}) are defined in the text.

Values are group means with standard errors in parentheses.

ject values varied over a two- to sixfold range, reflecting large intersubject variation in the triexponential coefficients.

At each dose, the "intercompartmental" transfer rate constant k_{31} was much lower than k_{21} and k_{10} (elimination rate constant). In the context of a three-compartment mammillary model (Figure 2), this indicates that movement of hydromorphone from a set of tissues (V_B) that slowly equilibrates with blood governs the rate of terminal elimination of the opioid after an intravenous bolus dose.

In Table 4, we present a comparison of plasma hydromorphone concentrations (for the 40-μg/kg dose) measured by high-performance liquid chromatography in this study and as measured by two different radioimmunoassay methods in previously reported studies using 2-mg intravenous doses (corresponding to 23.2 μg base/kg in Vallner et al. [6] and 25.8 μg base/kg in Parab et al. [7]) for selected times after the bolus doses. In each of the previous studies using radioimmunoassays, measured hydromorphone concentrations were higher than those produced by an even larger dose of the opioid when concentrations are measured by high-performance liquid chromatography (this study).

Discussion

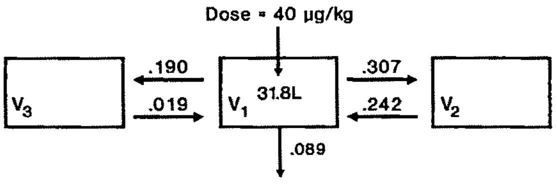
In all subjects at all doses, we found three distinct phases of hydromorphone loss from plasma after intravenous bolus injections. The first phase (π) has not been characterized previously. In contrast to previous studies, we were able to define this "fast distributional" phase by sampling blood frequently at early times after hydromorphone injections. Distributional properties of hydromorphone are very similar

Table 3. Pharmacokinetic Parameters for Three Doses of Hydromorphone

	10 μg/kg	20 μg/kg	40 μg/kg	*P*	Pooled mean
$t_{1/2\pi}$ (min)	1.40 (0.17)	1.13 (0.12)	1.25 (0.16)	0.624	1.27 (0.08)
$t_{1/2\alpha}$ (min)	16.2 (2.7)	13.2 (2.3)	14.3 (3.2)	0.724	14.7 (1.5)
$t_{1/2\beta}$ (min)	208.0 (34.0)	182.6 (20.6)	162.0 (23.6)	0.171	184.2 (15.0)
Cl (L/min)	1.51 (0.30)	1.61 (0.19)	1.85 (0.20)	0.303	1.66 (0.13)
V_c (L)	26.2 (4.2)	22.8 (2.2)	26.2 (3.7)	0.476	24.4 (2.0)
Vd_{ss} (L)	283 (24)	300 (20)	301 (24)	0.702	295 (13)
k_{12}	0.260 (0.039)	0.322 (0.043)	0.307 (0.052)	0.804	0.296 (0.025)
k_{21}	0.110 (0.018)	0.143 (0.023)	0.142 (0.023)	0.850	0.131 (0.011)
k_{13}	0.153 (0.026)	0.194 (0.025)	0.190 (0.043)	0.706	0.179 (0.018)
k_{31}	0.017 (0.002)	0.017 (0.003)	0.019 (0.002)	0.888	0.018 (0.001)
k_{10}	0.071 (0.013)	0.079 (0.008)	0.089 (0.019)	0.874	0.0080 (0.008)

$t_{1/2\pi}$ and $t_{1/2\alpha}$ are distributional half-lives and $t_{1/2\beta}$ is the elimination half-life; Cl_s = systemic clearance. V_c and Vd_{ss} are central compartment and steady-state distribution volumes, respectively. k_{12}, k_{21}, k_{13}, and k_{31} are first-order intercompartmental transfer rate constants (min^{-1}) between the central and shallow or deep compartments. k_{10} = elimination rate constant (central compartment).

Means and standard errors of individual subject values for each dose level are presented along with mean values for all subjects at all doses.



$$C_p = 89.7e^{-.67t} + 9.53e^{-.07t} + 4.54e^{-.005t}$$

Figure 2. Compartmental model for hydromorphone distribution and elimination (40 μg/kg IV). V_1 represents the central compartment (Vc in text).

Table 4. Comparison of Hydromorphone Plasma Concentrations (ng/mL) at Selected Times After Intravenous Bolus Doses

Time (min)	Vallner et al. (6) (23.2 μg/kg)	Parab et al. (7) (25.8 μg/kg)	Hill et al.[a] (40 μg/kg)
15	28	20	7
30	20	9	5
60	18	5	4
120	13	3	2.5

[a] The present study.

to those reported for morphine (15–17). We found that about 90% of hydromorphone is lost from plasma within 10 min after a 45-s injection. This rapid loss of hydromorphone from blood presumably to highly perfused tissues occurs with a mean hybrid rate constant of 0.636/min, about 10 times more rapidly than redistribution to other tissues (α = 0.063/min). It should be noted that because we used forearm venous sampling here, initial local drug distribution may have accounted for some systemic drug loss during the early sampling period. Also, we used a brief infusion (45 s) instead of a true bolus delivery for the hydromorphone injections and that may also limit the accuracy of the estimations of initial hydromorphone distribution characteristics. Nonetheless, this apparent initial phase of rapid redistribution of hydromorphone is similar to that of morphine after intravenous bolus doses with peripheral venous sampling in normal volunteers (18) and in cancer patients with central venous sampling (19).

Comparison of the intercompartmental transfer rate constants and elimination rate constants indicates that the rate of diffusion of hydromorphone from one of the tissue "compartments" to plasma governs the terminal elimination of hydromorphone from the body ($k_{31} << k_{21}, k_{10}$). This dependence of hydromorphone elimination on extensive tissue uptake and slow release of hydromorphone from tissue to blood is very similar to the kinetic behavior of morphine (15), fentanyl (20), and methadone (21), in contrast to alfentanil, which distributes less extensively from plasma to tissues than do other μ-receptor agonists (22).

Our findings with hydromorphone present a further example of the substantial pharmacokinetic variability across subjects that is characteristic of opioids. The triexponential coefficients varied over a two- to eightfold range in this group of subjects. This is very similar to the large intersubject pharmacokinetic variability reported for meperidine (23), morphine (16), fentanyl (24), alfentanil (20), and nalbuphine (17). This pharmacokinetic variability probably contributes importantly to the variable clinical response to a fixed dose of hydromorphone. The results of this study reinforce the desirability of administering hydromorphone on the basis of individual patient need for pain relief instead of using a standard dose for pain control. As with other opioids, use of hydromorphone via patient-controlled analgesia techniques should obviate or diminish the impact of pharmacokinetic variability on adequate dosing.

In the two previous studies of hydromorphone pharmacokinetics, radioimmunoassays using morphine antibodies were employed to measure plasma hydromorphone concentrations. Catlin (25) demonstrated substantial variation in cross-reactivity of different batches of radioimmunoassay antibody with morphine and its glucuronide metabolites. Unlike radioimmunoassay, the high-performance liquid chromatography method used in this study does not detect morphine glucuronides (or normorphine) as morphine. The higher plasma concentrations found at each time point by radioimmunoassay may be due to antibody cross-reactivity with hydromorphone metabolites (e.g., hydromorphone-3-glucuronide). The glucuronide metabolites of morphine have longer elimination half-lives and lower clearances and volumes of distribution than morphine (26,27). If the same is true of hydromorphone glucuronides, then the pharmacokinetic parameters reported earlier for this opioid would be expected to differ from those reported here.

Pharmacokinetic linearity with dose is a very desirable feature relevant to clinical use of opioids and should be examined routinely in pharmacokinetic studies (28). Hydromorphone pharmacokinetics are not dose-dependent over the fourfold range of doses studied here. This is similar to results reported for morphine (15) and other opioids (20,21). Our estimation of terminal elimination rate constants and terminal half-life could be inaccurate because the last blood samples were obtained only 5 h after the hydromorphone doses. However, the excellent fits of each subject's data and the grouped data at each dose (see Figure 1) by the triexponential model employed here during the 90–300-min period indicate that this does represent the terminal elimination phase for hydromorphone. Half-lives determined by separately fitting monoexponential equations to the 90–300-min data sets of the individual subjects were very similar to the terminal elimination half-lives ($t_{1/2\beta}$ values) derived from the triexponential equations, indicating further that either the latter are valid estimates or a terminal hydromorphone elimination phase exists that does not begin to be evident until more than 5 h after dosing.

We are beginning to understand the relationship between plasma opioid concentration, analgesic effects, and side-effect liabilities for opioid analgesics that are selective μ-receptor agonists (18,29,30). For hydromorphone, Reidenberg et al. (8) reported that the minimally effective plasma concentration in patients with chronic severe pain is about 4 ng/mL. In studies using continuous hydromorphone infusions in patients with cancer pain, Inturrisi et al. (31) found that half-maximal pain relief was produced by a plasma hydromorphone concentration of about 20 ng/mL (Css_{50}), whereas the Css_{50} for sedation was about twice that value. However, in both of these studies there was considerable intersubject variability in the pharmacokinetic-pharmacodynamic relationships. Steady-state studies are needed to clarify the relationship between plasma hydromorphone concentration and magnitudes of pharmacologic effects (18,30); these have not yet been done.

We thank Dr. Gary Donaldson for performing statistical analyses for this study and Kathy Andrus for expert assistance with the hydromorphone assays.

References

1. Mahler DL, Forrest WH Jr. Relative analgesic potencies of morphine and hydromorphone in postoperative pain. Anesthesiology 1975;42:602–7.
2. Hanna C, Mazuzan JE Jr, Abajian J Jr. An evaluation of dihydromorphinone in treating postoperative pain. Anesth Analg 1962;41:755–61.
3. Roy SD, Flynn GL. Solubility and related physicochemical properties of narcotic analgesics. Pharm Res 1988;5:580–6.
4. Parab PV, Coyle DE, Streng WH, Denson DD, Ritschel WA. Biopharmaceutic parameters of hydromorphone and in-vitro evaluation of its tablet and suppository dosage form. Pharm Ind 1987;49:951–6.
5. Cone EJ, Phelps BA, Gorodetzky CW. Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs, and rabbits. J Pharm Sci 1977;66:1709–13.
6. Vallner JJ, Stewart JT, Kotzan JA, Kirsten EB, Honigberg IL. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. J Clin Pharmacol 1981;21:152–6.
7. Parab PV, Ritschel WA, Coyle DE, Gregg RV, Denson DD. Pharmacokinetics of hydromorphone after intravenous, peroral and rectal administration to human subjects. Biopharm Drug Dispos 1988;9:187–99.
8. Reidenberg MM, Goodman H, Erle H, et al. Hydromorphone levels and pain control in patients with severe chronic pain. Clin Pharmacol Ther 1988;44:376–82.
9. Kerr IG, Sone M, DeAngelis C, Iscoe N, MacKenzie R, Schueller T. Continuous narcotic infusion with patient-controlled analgesia for chronic cancer pain in outpatients. Ann Intern Med 1988;108:554–7.
10. Coda B, Tanaka A, Hill H, Iverson K. Dose effects of hydromorphone in human analgesia. Pain 1990;(Suppl 5):S189.
11. Todd RD, Muldoon SM, Watson RL. Determination of morphine in cerebrospinal fluid and plasma by high performance liquid chromatography with electrochemical detection. J Chromatogr Biomed Appl 1982;232:101–10.
12. Knott GD. Mlab—a mathematical modeling tool. Comput Programs Biomed 1979;10:271–80.
13. Akaike H. Fitting autoregressive models for prediction. Ann Inst Stat Math 1969;21:243–7.

14. Gibaldi M, Perrier D, eds. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982.

15. Murphy MR, Hug CC Jr. Pharmacokinetics of intravenous morphine in patients anesthetized with enflurane-nitrous oxide. Anesthesiology 1981;54:187–92.

16. Stanski DR, Greenblatt DJ, Lappas DG, Koch-Wester J, Lowenstein E. Kinetics of high-dose intravenous morphine in cardiac surgery patients. Clin Pharmacol Ther 1976;19:752–6.

17. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose I.V. morphine in normal volunteers and patients with end-stage renal failure. Br J Anaesth 1984;56:813–9.

18. Hill HF, Saeger L, Bjurstrom R, Donaldson G, Chapman CR, Jacobson R. Steady-state infusions of opioids in human volunteers. I. Pharmacokinetic tailoring. Pain 1990;43:57–67.

19. Hill HF, Jacobson RC, Coda BA, Mackie AM. A computer-based system for controlling plasma opioid concentrations according to patient need for analgesia. Clin Pharmacokinet (in press).

20. Bower S, Hull CJ. Comparative pharmacokinetics of fentanyl and alfentanil. Br J Anaesth 1982;54:871–8.

21. Nilsson MI, Meresaar U, Angaard E. Clinical pharmacokinetics of methadone. Acta Anaesthesiol Scand 1982;74:66–9.

22. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. Clin Pharmacokinet 1983;8:422–46.

23. Austin KL, Stapleton JV, Mather LE. Relationship between blood meperidine and analgesic response: a preliminary report. Anesthesiology 1986;53:460–6.

24. Reilly CS, Wood AJ, Wood M. Variability of fentanyl pharmacokinetics in man. Anaesthesia 1984;40:837–43.

25. Catlin DH. Pharmacokinetics of morphine by radioimmunoassay: the influence of immunochemical factors. J Pharmacol Exp Ther 1977;200:224–35.

26. Sawe J. Kager L, Svensson Eng J-O, Rane A. Oral morphine in cancer patients: in vivo kinetics and in vitro hepatic glucuronidation. Br J Clin Pharmacol 1985;19:495–501.

27. Osborne R, Joel S, Trew D, Slevin M. Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. Clin Pharmacol Ther 1990;47:12–9.

28. Van Rossum JM, van Lingen G. Dose-dependent pharmacokinetics. In: Rowland M, Tucker G, eds. International encyclopedia of pharmacology and therapeutics, section 122.

29. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ. Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 1988;67:329–37.

30. Hill HF, Chapman CR, Saeger L, et al. Steady-state infusions of opioids in human. II. Concentration-effect relationships and therapeutic margins. Pain (in press).

31. Inturrisi C, Portenoy R, Stillman M, Colburn W, Foley K. Hydromorphone bioavailability and pharmacokinetic-pharmacodynamic (PK-PD) relationships. Am Soc Clin Pharmacol Ther 1988;43:162.

Low-Dose Bupivacaine Does Not Improve Postoperative Epidural Fentanyl Analgesia in Orthopedic Patients

Neal H. Badner, MD, Eleanor J. Reimer, MD, Wendy E. Komar, RN,
and Carol A. Moote, MD

BADNER NH, REIMER EJ, KOMAR WE, MOOTE CA. Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. Anesth Analg 1991;72:337–41.

Epidural infusions of 10 µg/mL fentanyl combined with low-dose bupivacaine (0.1%) were compared with epidural infusions of fentanyl alone for postoperative analgesia after total knee joint replacement. There were no detectable differences between the two groups in analgesia (visual analogue scale ranging between 15 and 40 mm), infusion rates (which averaged 7–9 mL/h), or serum fentanyl levels (which reached 1–2 ng/mL). The incidence of side effects, including nausea, vomiting, and pruritus, was also similar. Of the patients receiving fentanyl and low-dose bupivacaine, one developed a transient unilateral motor and sensory loss, and one developed significant hypotension and respiratory depression. The addition of low-dose bupivacaine does not improve epidural fentanyl infusion analgesia after knee surgery and may increase morbidity.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—fentanyl with and without bupivacaine. PAIN, POSTOPERATIVE. ANALGESICS, FENTANYL. ANESTHETICS, LOCAL—bupivacaine.

A major advance in the treatment of postoperative pain has been the use of epidural narcotics, primarily morphine, usually by intermittent injection (1,2) or, more recently, by continuous infusion (3,4). These techniques have provided improved analgesia and postoperative pulmonary function when compared with intravenous morphine injections (2). Side effects, however, include respiratory depression, pruritus, and urinary retention, as well as nausea and vomiting. This has led to the use of lipid-soluble narcotics such as fentanyl. When given as a continuous infusion, epidural fentanyl is effective for postoperative pain relief with lower incidences of pruritus, nausea, and vomiting (5–7) and may not cause clinically significant respiratory depression (6–9). Patients given continuous epidural infusions of fentanyl may, however, develop plasma fentanyl concentrations ranging from 1 to 2 ng/mL (9), concentrations that have been shown to depress the carbon dioxide ventilatory response curve (8,10). Efforts to decrease the dosage and therefore limit the systemic absorption of fentanyl are hence desirable.

More recently, epidural infusions of narcotic and low-dose bupivacaine have been used. Theoretically, because the two drugs act by different mechanisms, their effects should be additive. This should therefore allow decreased amounts of each drug to be administered and thereby minimize the incidence of side effects. Side effects associated with bupivacaine include sympathetic blockade and resulting postural hypotension, as well as sensory and motor blockade yielding discomfort or difficulty with ambulation. Initially bupivacaine was combined with morphine, but the combination was no better than an infusion of epidural morphine alone in terms of analgesia, total narcotic requirements, and the incidence of nausea or pruritus after either thoracotomy (4) or upper abdominal surgery (11). Recently, epidural infusions of fentanyl and low-dose bupivacaine have been shown to be effective for postoperative pain management (12–15), although the dosages of fentanyl used may have been sufficient to supply analgesia alone. To our knowledge no study has compared the combination of fentanyl and low-dose bupivacaine as an epidural infusion with an infusion of epidural fentanyl alone, in a double-blind, randomized fashion, as we have

---

Received from the Department of Anaesthesia, University Hospital, University of Western Ontario, London, Ontario, Canada. Accepted for publication November 2, 1990.

Address correspondence to Dr. Badner, Department of Anaesthesia, University Hospital, 339 Windermere Road, London, Ontario N6A 5A5, Canada.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Demographic Data

	Fentanyl	Fentanyl and bupivacaine
Age (yr)	69 ± 5	65 ± 6
Weight (kg)	84 ± 15	90 ± 16
Height (cm)	174 ± 10	167 ± 11
Sex (male/female)	11/3	6/10
n	14	16

Except for *n* and sex, values are expressed as mean ± SD.
No significant differences existed.

done in patients having undergone elective total knee joint replacement.

Methods

After institutional approval and written informed consent, patients who were to undergo elective total knee joint replacement under epidural anesthesia were considered for study. Patients older than 75 yr, with a weight greater than 100 kg, or with significant cardiac, renal, hepatic, or cerebrovascular disease, preexisting motor or sensory deficit, or psychiatric history were excluded from the study.

Preoperatively, patients had an epidural catheter inserted at the L2-3 or L3-4 intervertebral space. Intraoperatively, patients were monitored in the routine fashion. Anesthesia was produced using 0.5% bupivacaine and/or 2% CO_2 lidocaine via the epidural catheter at the discretion of the attending anesthetist. Postoperatively, on return of motor function a continuous epidural infusion was initiated with 6 mL/h of a coded syringe using a standardized syringe pump. The infusion syringes were prepared as a solution with a fentanyl concentration of 10 μg/mL with or without addition of 1 mg/mL (0.1%) bupivacaine.

Postoperatively, patients remained in the recovery room for 2–3 h and then were transferred to the orthopedic floor. Blood pressure and heart rate were recorded every 4 h, and respiratory rate was monitored hourly during the next 48 h. Patients were also assessed for level of analgesia using a visual analogue scale (VAS; 0 = no pain and 100 = worst pain ever), and for the presence of nausea, vomiting, pruritus, motor blockade, or a sensory level to pinprick or temperature. These measurements were made before recovery room departure, later that afternoon (POD0PM), on the morning of the first and second postoperative days (POD1AM, POD2AM), and on the afternoon of the first postoperative day (POD1PM). If at any time the pain score was >33, a bolus dose of 3 mL of the study solution was given epidurally and the infusion was increased by 2 mL/h. If at any time after recovery room departure the patient was drowsy and/or somnolent the infusion rate was decreased by 2 mL/h.

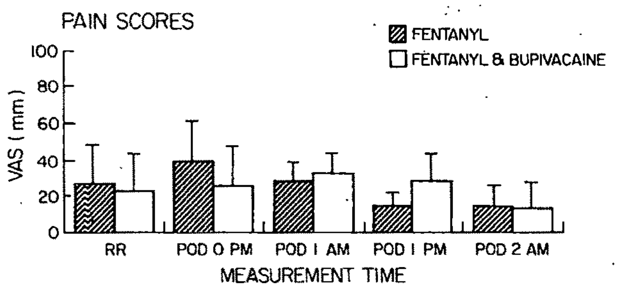


Figure 1. Pain scores (visual analogue scale) at the five measurement times. Values are mean ± SD. No significant differences were detected. RR, recovery room departure.

Venous samples for analysis of serum fentanyl levels were taken at the same time intervals as above using a heparin lock catheter. Samples were centrifuged and stored at −20°C until fentanyl analysis was performed using a commercial radioimmunoassay kit (16) (Janssen Laboratories, Beerse, Netherlands).

Demographic comparisons were made using unpaired *t*-tests for parametric data and χ^2 analysis for nonparametric data. Infusion rates and VASs were compared using two-factor analysis of variance for repeated measures. Side effects were compared with χ^2 analysis.

Results

Thirty ASA physical status I–III patients undergoing elective total knee joint repair were studied. Their demographic data are summarized in Table 1. There were no statistically significant differences in the age, weight, height, or sex distribution between those patients given epidural fentanyl alone and those given epidural fentanyl combined with bupivacaine. Four patients, two from each group, were removed from the study during the first postoperative day because of catheter dislodgement diagnosed by physical examination or testing with 2% CO_2 lidocaine.

The average pain scores at the different measurement times are shown in Figure 1. The mean pain scores ranged between 15 and 40 mm during the study period. There were no statistically or clinically significant differences between either group at any of the measurement times. The average infusion rates in each group are shown in Figure 2. After recovery room departure, the infusion rates averaged 7–9 mL/h over the next 48 h. Again, there were no statistically or clinically significant differences in

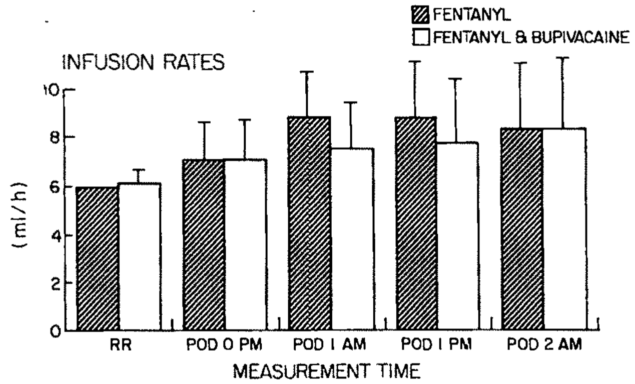


Figure 2. Epidural infusion rates at the five measurement times. Values are mean ± SD. No significant differences were present. RR, recovery room departure.

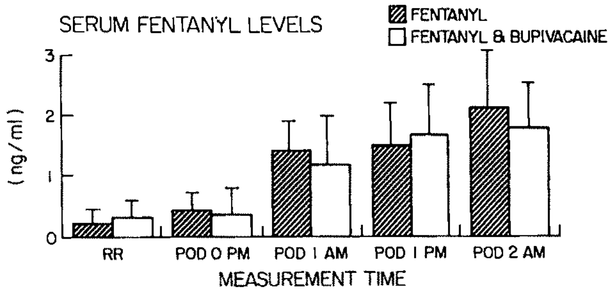


Figure 3. Serum fentanyl levels during the study period. Values are mean ± SD. No significant differences were found. RR, recovery room departure.

mean infusion rates between patients receiving epidural fentanyl and those receiving epidural fentanyl and bupivacaine. Assuming that a clinically significant difference in pain scores is 20 mm, or in infusion rates is 2 mL/h, and with the use of an appropriate power table, one finds that the power of this study is 0.90.

The average serum fentanyl levels are shown in Figure 3. The mean values increased above 1 ng/mL after 24 h and reached approximately 2 ng/mL after 48 h. There were no differences between the groups at any of the measurement times.

The incidences of nausea, vomiting, and pruritus are listed in Table 2. There were no statistically significant differences in the incidences of any of these side effects at any of the measurement times between the two kinds of epidural infusion. There was a trend to a higher incidence of nausea and vomiting on the first postoperative day in patients receiving the fentanyl and bupivacaine mixture. This was invariably mild, and it responded to intramuscular diphenhydramine. One patient in the fentanyl and bupivacaine group developed a unilateral motor and sensory loss involving the L3-4 dermatome for the 48-h study period, which resolved on discontinuation of the epidural infusion. Another patient in the fentanyl and bupivacaine group developed significant hypotension and respiratory depression (respiratory rate = 6–8 breaths/min) that required treatment with intravenous crystalloid and 0.4 mg intravenous naloxone.

Discussion

Although there have been several reports of the use of epidural infusions of fentanyl and low-dose bupivacaine (13–15), none of them have been double-blind or randomized. As the dosages of fentanyl used with bupivacaine in these studies were similar to those used in studies using infusions of epidural fentanyl alone (8,17), we believed a double-blind study was necessary. We chose patients who were undergoing total knee replacement as they made up 31% of the patients in the study by Lubenow et al. of epidural fentanyl-bupivacaine infusion (15) and because they were a relatively homogeneous group of patients that would allow optimum randomization.

We were able to obtain pain scores in our postoperative orthopedic patients similar to those acquired in studies using epidural infusions of fentanyl combined with bupivacaine (13–15) or those using fentanyl alone (8,17). In addition, the infusion rates that our patients required were similar to those used in these other studies while using identical fentanyl and/or bupivacaine concentrations. We believe that a clinically significant difference in the VAS of 20 mm or 2 mL/h in infusion rates would be necessary to warrant using the fentanyl-bupivacaine combination, and the power of this study is therefore sufficient to support our conclusions. The incidence of side effects was higher in the present study than that reported by others (13–15) who used fentanyl and bupivacaine, but is similar to data reported for hydromorphone (18) as well as for diamorphine (19) combined with bupivacaine. We therefore feel confident of our conclusion that the addition of low-dose bupivacaine neither improves postoperative analgesia nor decreases the incidence of side effects in orthopedic patients.

Why the addition of low-dose bupivacaine to epidural fentanyl is not efficacious in orthopedic patients is not clear. The fact that the mean plasma fentanyl levels in both groups were not different at any of the measurement times, while at the same time being consistent with studies using epidural fentanyl infusions alone (8,9,20), implies that the bupivacaine is not inhibiting epidural fentanyl uptake.

Table 2. Incidence of Side Effects

	Fentanyl			Fentanyl and bupivacaine		
Time	Nausea	Vomiting	Pruritus	Nausea	Vomiting	Pruritus
RR	14	7	0	31	13	6
POD0PM	46	23	15	31	15	38
POD1AM	29	23	21	62	46	46
POD1PM	42	0	25	67	55	42
POD2AM	20	10	60	45	8	17

RR, recovery room departure; POD0PM, later in the afternoon after surgery; POD1AM, first postoperative day in the morning; POD1PM, first postoperative day in the afternoon; and POD2AM, second postoperative day in the morning.

No significant differences were detectable.

We believe that the 0.1% concentration of epidural bupivacaine is simply insufficient to offer an advantage in the patient population we studied. Raj et al. (21) used epidural infusions of bupivacaine alone to provide postoperative analgesia to total knee joint replacement patients and needed 6–15 mL/h of a 0.25% solution. All their patients had sensory losses, and most had motor deficits, which is presumably why investigators using the narcotic-bupivacaine combination have chosen the lower dosage of 0.1%. Also, most of the patients in the studies using the combination of epidural fentanyl and bupivacaine infusions have had thoracic or abdominal procedures. Visceral pain fibers run in association with sympathetic fibers, and there is therefore a much higher proportion of smaller, unmyelinated fibers (22) that can be more readily blocked by local anesthetics. This may allow the low concentration of 0.1% bupivacaine to be effective in this population as opposed to our patients after knee joint replacement. This hypothesis is supported by findings in obstetric patients in which infusions of fentanyl (18,23,24), sufentanil (23,25), and alfentanil (23) mixed with 0.125% bupivacaine supplied analgesia superior to that provided by infusions of bupivacaine alone. These studies are not entirely comparable to ours, however, as their patients were experiencing labor pain, which is not relieved by narcotics alone (26), and because comparisons were made with bupivacaine alone rather than with fentanyl alone.

A recent report that continuous epidural infusions of hydromorphone and 0.08% bupivacaine are no more beneficial than hydromorphone alone for pain after cesarean section (27) is consistent with earlier studies using morphone. When morphine alone was compared with morphine and bupivacaine as epidural infusions in patients after a thoracotomy (4) or in patients after abdominal surgery (11), no difference in analgesia or side effects was found. In addition, the only other double-blind study claiming beneficial effects of adding low-dose bupivacaine to an epidural narcotic infusion, in this case diamorphine after hysterectomy, used such high infusion rates that all patients developed motor and sensory deficits and all patients required supplemental analgesia (19). These findings are consistent with ours and call into question the use of low-dose bupivacaine with epidural fentanyl for visceral postoperative pain as well.

In summary, we have shown that using similar infusion rates epidural infusions of fentanyl provide analgesia equal to that provided by epidural infusions of fentanyl and low-dose bupivacaine without any difference in the incidence or type of side effects, in patients having total knee joint replacement. To ascertain whether visceral pain is different and more amenable to epidural infusions of fentanyl and bupivacaine will require further studies in appropriate patients.

The authors wish to thank Kelly Brown for her secretarial assistance.

References

1. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;59:473–80.
2. Shulman M, Sandler AN, Bradley JW, Young PS, Brebner J. Post-thoracotomy pain and pulmonary function following epidural and systemic morphine. Anesthesiology 1984;61:569–75.
3. El-Baz NMI, Faber LP, Jensik RJ. Continuous epidural infusion of morphine for treatment of pain after thoracic surgery: a new technique. Anesth Analg 1984;63:757–64.
4. Logas WG, El-Baz N, El-Ganzouri A, et al. Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. Anesthesiology 1987;67:787–91.
5. Bailey PW, Smith BE. Continuous epidural infusion of fentanyl for postoperative analgesia. Anaesthesia 1980;35:1002–6.
6. Bell SD, Berman R, Ensalada L. The use of continuous lumbar epidural fentanyl for post-operative pain relief in thoracotomies. Can J Anaesth 1988;35:S112–3.
7. Bell SD, Berman R, Ensalada L. The use of continuous lumbar epidural fentanyl for post-operative pain relief in thoracotomies Reg Anesth 1988;13:1S.

8. Renaud B, Brichant JF, Clergue F, Chauvin M, Levron JC, Viars P. Ventilatory effects of continuous epidural infusion of fentanyl. Anesth Analg 1988;67:971–5.
9. Badner NH, Sandler AN, Leitch LF, Koren G. Analgesic and respiratory effects of continuous lumbar epidural fentanyl infusions in post-thoracotomy patients. J Thorac Cardiovasc Anesth 1990;4:543–51.
10. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A. Ventilatory depression related to plasma fentanyl concentrations during and after anaesthesia in humans. Anesth Analg 1983;62:966–74.
11. Cullen ML, Staren ED, El-Ganzouri A, Logas WG, Ivankovich AD, Economou SG. Continuous epidural infusion for analgesia after major abdominal operations: a randomized, prospective, double-blind study. Surgery 1985;98:718–28.
12. Guillen JC, Ragi J, Brugueralle B, Levron JC, Martin C. Continuous thoracic epidural analgesia for 5 days: clinical and plasma evaluation. Anesthesiology 1988;69:A404.
13. Fisher R, Lubenow T, Licega A, McCarthy RJ, Ivankovich AD. Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. 1988;67:559–63.
14. Lubenow TR, Wong J, McCarthy RJ, Ivankovich AD. Prospective evaluation of continuous epidural narcotic-bupivacaine infusions in 1500 postoperative patients. Reg Anesth 1989; 14(2S):32.
15. Lubenow TR, Wong J, McCarthy RJ, Logas WG, Ivankovich AD. Prosepctive evaluation of continuous epidural narcotic-bupivacaine infusions in 1000 patients. Anesthesiology 1988; 69:A389.
16. Michiels M, Hendriks R, Heykants J. A sensitive radioimmunoassay for fentanyl plasma levels in dogs and man. Eur J Clin Pharmacol 1977;12:153–8.
17. Loper KA, Ready LB, Downey M, et al. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. Anesth Analg 1990;70:72–5.
18. Elliot RD, Stockwell M. Continuous infusion epidural anaesthesia for obstetrics bupivacaine vs bupivacaine-fentanyl. Can J Anaesth 1990;37:S6.
19. Lee A, Simpson D, Whitfield A, Scott DB. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. Br J Anaesth 1988;60:845–50.
20. Chrubasik J, Wust H, Schute-Monting J, et al. Relative analgesic potency of epidural fentanyl, alfentanil and morphine in treatment of postoperative pain. Anesthesiology 1980;68:929–33.
21. Raj PP, Knarr DC, Vigdoth E, et al. Comparison of continuous epidural infusion of a local anesthetic and adminstration of systemic narcotics in the management of pain after total knee replacement surgery. Anesth Analg 1987;66:401–6.
22. Bonica JJ. Anatomic and physiologic basis of nociception and pain. In: Bonica JJ, ed. The management of pain. 2nd ed. Philadelphia: Lea & Febiger, 1990:28–45.
23. Wilhite AO, Blass NH. Comparison of analgesic efficacy of alfentanil, fentanyl, and sufentanil in continuous epidural infusions of 0.125% bupivacaine for labor and delivery. Anesthesiology 1989;71:A902.
24. Skerman JH, Thompson BA, Goldstein MT, Jacobs MA, Gupta A, Blass NH. Combined continuous epidural fentanyl and bupivacaine in labour: a randomized study. Anesthesiology 1985;63:A450.
25. Phillips G. Continuous infusion epidural analgesia in labor: the effect of adding sufentanil to 0.125% bupivacaine. Anesth Analg 1988;67:422–5.
26. Carrie IES, O'Sullivan GM, Leeglobin R. Epidural fentanyl in labour. Anesthesia 1981;36:965–9.
27. Parker RK, Baron M, Helfer DC, Berberich N, White PF. Use of epidural PCA for postoperative pain management: effect of local anesthetic on the opioid requirement (abstract). Anesth Analg 1990;70:S297.

Long-Latency Auditory Evoked Potentials During General Anesthesia: N1 and P3 Components

G. Plourde, MD, MSc, and T. W. Picton, MD, PhD

PLOURDE G, PICTON TW. Long-latency auditory evoked potentials during general anesthesia: N1 and P3 components. Anesth Analg 1991;72:342–50.

The N1 and P3 auditory evoked potentials were recorded to evaluate their usefulness as measures of the level of consciousness in 14 ASA physical status I and II patients undergoing elective surgery. The anesthetic agents were thiopental, fentanyl, and isoflurane with or without nitrous oxide. Recordings were carried out before induction (preinduction) and during induction, surgical anesthesia, emergence, and recovery from anesthesia. The auditory response was evoked by 700-Hz tones that occurred occasionally and unpredictably in a train of 500-Hz tones delivered at 40 per second. The patients were asked to press a button whenever they detected a 700-Hz tone. Studies with normal subjects have repeatedly shown that detected tones (HITS) evoke N1 and P3 waves, whereas undetected tones (MISSES) evoke no recognizable waves. The responses evoked by HITS were compared with those evoked by MISSES. The amplitudes of N1 and P3 were significantly different from zero for HITS before induction and during induction and recovery but not during emergence. The amplitudes of N1 and P3 were not different from zero for MISSES during induction, surgery, and emergence. During recovery, the N1 and P3 for MISSES were small and the P3 for HITS was significantly larger than for MISSES. The results indicate that except during emergence, HITS were associated with clear N1 and P3 waves, whereas MISSES were not. The lack of either N1 or P3 for HITS during emergence perhaps occurred because the patients, although responsive, were not yet fully conscious. The N1 and P3 components of the auditory evoked potential may provide specific indicators for consciousness.

Key Words: ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—isoflurane. BRAIN, AUDITORY EVOKED RESPONSES—electroencephalography. MONITORING, ELECTROENCEPHALOGRAPHY.

There is at present no satisfactory method to detect unintentional intraoperative awareness. Clinical signs are nonspecific and are frequently obscured by muscle relaxants and autonomic drugs (1). The electroencephalogram may sometimes indicate that a patient is unconscious (e.g., burst suppression or isoelectricity), but it cannot indicate when and if a patient is conscious (2–6). An α-pattern (similar to the normal α-rhythm of conscious subjects) can be seen in anesthetized patients and widespread δ-activity (similar to that seen in sleep, anesthesia, or coma) can be seen in conscious patients (7).

Sensory evoked potentials (EPs) may provide more specific information about consciousness. Evoked potentials can be classified as exogenous or endogenous (8). Exogenous EPs, which are mainly determined by the physical nature of the evoking stimulus, have frequently been recorded during anesthesia (9,10). Endogenous EPs generally occur after 100 ms, are sensitive to the psychological state of the subject, and are relatively independent of the physical nature of the stimulus. Endogenous EPs have a well-established role in the study of human cognition (8,11,12). The aim of this research was to study the endogenous EPs during changes in the level of consciousness with general anesthesia. Two components were considered: the N1 and the P3 (or P300).

The N1 auditory EP has a peak latency of 100 ms and is maximally recorded at the vertex. It displays some exogenous characteristics, being larger for more intense stimuli. The N1, however, has some endogenous characteristics in that it varies with selective attention (12,13). When a subject is instructed to pay

---

Supported by a grant from the Medical Research Council to T. W. Picton and by a Fellowship from the Fonds de la Recherche en Santé du Québec to G. Plourde.

Presented in part at the June 1989 Meeting of the Canadian Anaesthetists' Society in Ottawa.

Address correspondence to Dr. Plourde, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

Received from the Human Neurosciences Research Unit, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5. Accepted for publication November 8, 1990.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

attention to stimuli presented to one ear and to ignore stimuli presented to the other ear, the amplitude of the N1 is larger for stimuli presented to the attended ear. In tasks where the subject only attends to one train of stimuli and the discriminations are easy, there is usually no effect of attention on the N1.

The P3 (or P300) is a parietocentral positive wave with a typical peak latency of 300 ms (range, 250–600 ms) (14). It is associated with the detection of "target" stimuli and is relatively independent of the sensory modality. The most common paradigm for eliciting the P3 requires the subject to attend to a train of regularly occurring stimuli in order to detect improbable, unpredictable target ("oddball") stimuli that differ from the standard stimuli (e.g., occasional high-frequency tones in a run of low-frequency tones). Requiring the subject to count in response to the targets is sufficient to elicit a P3. By contrast, the P3 is very small or absent when the subject ignores the targets. The subjects are often instructed to press a button in response to the target stimulus to allow the experimenter to determine whether the stimulus was detected or not. Elicitation of the P3, however, does not require motor action. Several investigators have suggested that the P3 is associated with access to consciousness (8,14,15).

We recorded the late auditory EPs before, during, and after general anesthesia (thiopental, fentanyl, isoflurane with or without nitrous oxide [N_2O]) in order to assess the relationship between the N1 and P3 and the level of consciousness as evaluated with a signal-detection task. The recording paradigm was first evaluated in unanesthetized subjects.

Methods

Subjects

The project was approved by the Institutional Research Ethics Committee. Written informed consent was obtained from all subjects. Ten normal unanesthetized subjects (seven men) were tested in the control phase of the study. The mean age was 31 yr (range, 23–43). All subjects were free of neurologic or otologic diseases. They were tested in a sound-attenuated, electrically shielded room. Fourteen patients (eight women) admitted for elective surgery were tested. The mean age was 36 yr (range, 21–61). All patients were free of neurologic or otologic disease. Surgical procedures consisted of plastic surgery (eight patients), orthopedic surgery (two patients), urological surgery (two patients), general surgery (one patient), and thoracic surgery (one patient).

Anesthetic Technique

Eleven patients were premedicated with diazepam (0.1 mg/kg) by mouth, 60–90 min preoperatively. Three patients received no premedication. Anesthesia was induced with thiopental (5 mg/kg). After loss of responsiveness, vecuronium (0.1 mg/kg) was used to facilitate tracheal intubation. The lungs were mechanically ventilated to maintain an end-tidal partial pressure of CO_2 of 30 mm Hg (mass spectrometry). Anesthesia was maintained with fentanyl (3 μg/kg) and isoflurane (0.5%–1.5% end-tidal) in O_2 (seven patients), or in N_2O (60% end-tidal) in O_2 (seven patients). Nasopharyngeal temperature was continuously monitored. Neostigmine (with glycopyrrolate) was used to reverse muscular paralysis 10 min before emergence.

Stimuli

Tonebursts (500 Hz, 15-ms duration, 5-ms rise/fall time, 90-dB peak sound pressure level [SPL]) were presented binaurally at a rate of 40 per second via TDH-49 earphones in the controls and via insert earphones (Etymotic Research, ER3A) in the surgical patients. The frequency was occasionally (10 per minute on average) increased to 700 Hz for 75 ms to produce target stimuli. The patients were required to press a button after target stimuli whenever possible. The paradigm was designed to allow recording of both the steady-state response to the 500-Hz tones (16) and the N1 and P3 waves to the target 700-Hz stimuli.

Recording

The electroencephalogram was recorded with gold-plated cup electrodes attached with saline gel and collodion. The interelectrode impedances were less than 5 kΩ (at 10 Hz). Three electrodes were placed according to the International 10–20 system (17) at frontal (Fz), central (Cz), and parietal (Pz) midsagittal scalp locations with the right mastoid (M2) as a common reference. Vertical eye movements (forehead-cheek) were also recorded. A fifth channel was used to monitor button presses up to 1480 ms after stimulus. Half-amplitude lower and upper cutoffs were 0.16–100 Hz with a −20 dB/decade roll-off.

The analog-to-digital epoch lasted 1490 ms with a sampling frequency of 688 Hz per channel. The interval between onset of epochs was 2000 ms. The probability of an epoch containing a target stimulus was 0.33. Epochs containing a target (beginning

10 ms after the onset of the epoch) were averaged separately for HITS (i.e., button press present) and MISSES (i.e., button press absent). Epochs contaminated by muscle activity or eye movements were rejected. The rejection level for controls was ±175 μV for all channels. For the anesthetized patients, the level was ±350 μV. Less stringent rejection criteria were used with the anesthetized patients because electroencephalographic changes caused by anesthetic agents would have caused excessive rejection.

Design

We initially tested awake control subjects to confirm that adequate responses could be obtained, that the amplitude of the P3 is increased by attention, and that no motor action is required. The following five (A–E) conditions assessed the effects of attention, task, and status of eyes (open/closed). In condition A, subjects kept their eyes closed and were required to press a button after each target stimulus and to count the number of target stimuli. In condition B, subjects kept their eyes closed and were required to count the number of target stimuli without pressing a button. In condition C, subjects kept their eyes closed and pressed a button after each target stimulus without counting the number of targets. Condition D was similar to condition A, except that the subjects kept their eyes open. For condition E, subjects read a book and ignored the target stimuli. (Condition D was required to rule out eyes opening as the cause of a difference between conditions E and A, B, or C.) There were two recording blocks for each condition. The order of conditions and replications was counterbalanced within and across subjects. Recordings for each condition were combined before measurement.

With anesthetized patients, recordings were obtained during the following periods: 30–90 min before induction (preinduction) and during induction, surgery, emergence, and recovery. Patients kept their eyes closed and were instructed to press a button after each target whenever possible (similar to condition C above). The injection of thiopental began 30 s after the beginning of the induction recording and lasted 1 min. Recordings during surgery were done at stable (over 10 min) concentrations of isoflurane: 0.5% end-tidal when administered with 60% N_2O and 1.15% end-tidal when administered in O_2 alone. After surgery, the trachea was extubated as soon as the patients were able to open their eyes on command. Emergence was defined as the 10-min period immediately after the return of the ability to open their eyes on command and was followed by recovery. Within each period, other than induction, multiple recordings were usually carried out. Recordings from each period for each patient were combined separately for HITS and MISSES before measurement. Recordings could not be obtained from all patients for all periods because of movements or shivering.

Statistical Analysis

Awake controls. The average waveforms were digitally filtered (0–30 Hz) before analysis. N1 was measured at Cz and defined as the most negative peak occurring 80–180 ms after stimulus. P3 was measured at Pz and defined as the most positive peak occurring 250–450 ms after stimulus. Amplitudes were measured relative to baseline (initial 10 ms of epoch).

The amplitude and latency measurements were submitted to one-way analyses of variance for repeated measures to assess the effects of the experimental conditions. The Geisser-Greenhouse adjustment of the level of significance was used for repeated measures analyses of variance (18,19). Tukey's HSD test (18) was used for post hoc comparisons.

Anesthetized patients. The combined waveforms were digitally filtered (0–10 Hz) before analysis. A narrower bandpass was used because the data were noisier than those from awake controls. Measurements based on averages of less than six epochs were excluded because of excessive variability. Average amplitudes over a latency range were used instead of peak measurements because many recordings did not reveal clearly recognizable waves. The amplitude of N1 was defined as the average amplitude at Cz from 100 to 200 ms after the stimulus. The amplitude of the P3 was the average amplitude at Pz from 300 to 400 ms after the stimulus.

The amplitude measurements for each period were first examined in regard to differences between the two groups of patients (i.e., isoflurane in O_2 vs isoflurane in N_2O/O_2). The differences were small, inconsistent across periods or patients, and not significant on *t*-tests ($P > 0.20$). The results from the two groups were therefore pooled. The pooled measurements were submitted to one-sample *t*-tests to determine whether a wave was present (i.e., whether the mean amplitudes were significantly different from zero). Paired one-tailed *t*-tests were then used to compare the amplitude for HITS and MISSES during induction and recovery. (During preinduction, sur-

Table 1. Awake Control Subjects—Amplitude (μV)

Condition			Measurements	
Code	Eyes	Task	N1 (Cz)	P3[a] (Pz)
A	Closed	Press and count	−7.1 (5.4)	7.3 (2.0)
B	Closed	Count only	−6.5 (5.9)	6.7 (2.4)
C	Closed	Press only	−8.4 (2.8)	6.0 (2.9)
D	Open	Press and count	−6.9 (4.3)	6.7 (3.0)
E	Open	Ignore (read)	−6.1 (3.8)	3.3 (1.4)

Values are expressed as the mean, with standard deviation given in parentheses. $n = 10$.

[a] Significant planned comparison E vs A–D, $P < 0.001$.

gery, and emergence, the number of observations for either HITS or MISSES was insufficient for testing.) Paired one-tailed t-tests were also used to compare the amplitude for HITS during preinduction with that of HITS during induction and recovery. (The number of HITS during emergence was too small for testing.)

t-Tests were used instead of analyses of variance because data could not be obtained from all patients for all periods. With both awake control subjects and anesthetized patients, the criterion for significance was $P < 0.05$ for the analyses of variance and $P < 0.01$ for all other tests to reduce the likelihood of spurious significance.

Results

Awake Control Subjects

The measurements are summarized in Table 1. The average waveforms for the 10 subjects are shown in Figure 1. The P3 amplitude was significantly ($P < 0.001$) smaller for the IGNORE condition (E) compared with the ATTEND conditions (A–D). There were no other significant amplitude differences, the amplitude of N1 being approximately the same under all recording conditions.

There was no significant latency difference. The average latency for N1 and P3 was 137 and 327 ms, respectively. The mean modal reaction time (conditions A, C, and D) was 272 ms.

Anesthetized Patients

Anesthetic management. The average interval between start of induction and extubation was 134 min (SD, 69). Recording in the recovery room was started on average 41 min (SD, 26; range, 10–79) after extubation and was completed 66 min (SD, 32; range, 23–114) after extubation.

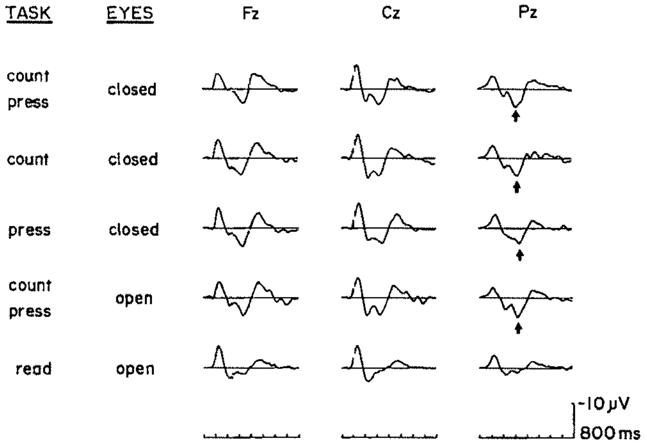


Figure 1. Grand mean responses from 10 control subjects during five different conditions. The amplitude of the P3 in the ATTEND conditions (i.e., press and/or count) is larger (*arrows*) than in the READ (IGNORE) condition where the P3 is very small. Recording from midfrontal (Fz), vertex (Cz), and midparietal (Pz) electrodes. Right mastoid was the reference for all channels. Negativity of the active electrode is plotted upward in this and all subsequent figures.

The mean nasopharyngeal temperature during surgery was 36.1°C (SD, 0.5; range, 35.4–37.0). The mean end-tidal partial pressure of CO_2 during surgery was 28 mm Hg (SD, 2.0; range, 27–33). For patients receiving isoflurane in N_2O, the mean end-tidal concentrations were 0.55% (SD, 0.12) and 62% (SD, 8), respectively. For patients receiving isoflurane in oxygen, the mean end-tidal concentration was 0.96% (SD, 0.08).

Evoked potentials. Measurements are summarized in Table 2. The number of observations varies because data could not be obtained from all patients for all periods either because patients could not be tested (movements, shivering), or because the averages had less than six epochs and were not measured.

The average waveforms for the 14 patients are shown in Figure 2. N1 is visible (downward arrows) for HITS during preinduction, induction, and recovery. There also seems to be a small N1 for MISSES during recovery. A P3 is present (upward arrows) for HITS during preinduction, induction, and recovery. For MISSES during recovery, there is a positive deflection in the P3 latency range, but it is too small for definitive interpretation. There were no recognizable waves for HITS during emergence, as well as for MISSES during induction, surgery, and emergence.

To determine the presence or absence of individual waves, t-tests (one-tailed) were used to find if the mean amplitudes were different from zero. The amplitudes of N1 and of P3 were significantly ($P < 0.01$) different from zero for HITS during preinduction,

Table 2. Anesthetized Patients

		Mean amplitude (μV)		
Period/type	n	N1 (100–200 ms) Cz	P3 (300–400 ms) Pz	Modal reaction time (ms)
Preinduction hits	14	−4.7 (4.0)[a]	4.0 (2.8)[a]	252 (64)
Induction hits	9	−3.2 (3.0)[a]	2.7 (1.6)[a]	322 (93)
Induction misses	12	1.7 (7.1)	0.2 (4.5)	—
Surgery misses	14	−0.6 (3.1)	0.2 (2.0)	—
Emergence hits	4	−0.8 (3.0)	−0.6 (2.4)	639 (174)
Emergence misses	10	−0.4 (1.8)	0.2 (1.1)	—
Recovery hits	12	−2.5 (2.5)[a]	2.9 (1.9)[a]	354 (124)
Recovery misses	7	−0.9 (1.2)	0.8 (1.2)	—

Values are expressed as the mean, with standard deviation given in parentheses. Total number of patients = 14. Data could not be obtained from all patients for all periods.

[a] Different from zero (one-tailed t-test, $P < 0.01$).

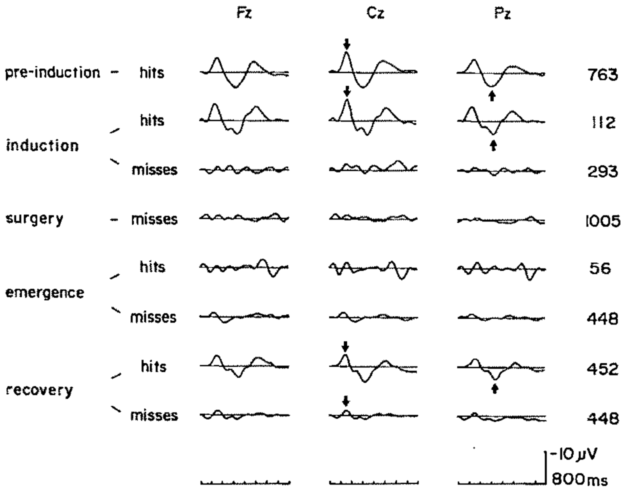


Figure 2. Grand mean waveforms from 14 patients pooled for each period and type of response. The number of epochs in each waveform is shown on the right. Note that there were no misses during preinduction and no hits during surgery. *Downward arrows* point to recognizable N1 waves at Cz. *Upward arrows* point to recognizable P3 waves at Pz.

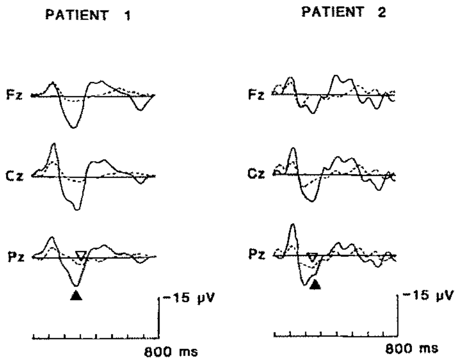


Figure 3. Recording from two patients during preinduction (*solid line*) and recovery (*dashed line*). Recovery readings were started 10 min after extubation and lasted 13 min. The N1 and P3 during recovery are smaller than during preinduction, but are clearly recognizable. The *filled triangles* indicate the P3 before induction; the *empty triangles* the P3 during recovery.

induction, and recovery. For MISSES during recovery, the amplitude of N1 and P3 nearly reached significance ($0.01 < P < 0.05$). The t-tests for MISSES during induction, surgery, and emergence as well as for HITS during emergence were not significant.

During induction and recovery, the amplitudes of N1 and P3 for HITS were larger than for MISSES. However, the difference was significant ($P < 0.01$) only for P3 and only during recovery. For preinduction, surgery, and emergence, the number of either HITS or MISSES was insufficient for similar comparisons.

The amplitude for HITS was significantly larger during preinduction than during recovery for N1 and P3 ($P < 0.01$).

The time-course of recovery of the EPs could not be examined in detail because of the 41-min mean interval between extubation and recovery recordings. For two patients, however, testing during recovery started 10 min after return of the ability to open the eyes on request and lasted 13 min. The N1 and P3 waves are clearly recognizable during recovery (Figure 3).

Discussion

Awake Subjects

The recordings were satisfactory and confirmed our expectations that the N1 amplitude would be the same for ATTEND (A–D) and IGNORE (E) conditions, whereas the amplitude of the P3 would be much larger for the ATTEND conditions.

The amplitude and latency of N1 were not affected by the recording conditions. Simple auditory attention does not usually affect the N1, provided that the level of arousal remains the same (8,13). The N1 amplitude is larger for attended than for nonattended stimuli when near-threshold intensities are used (20), when very difficult discriminations are required (21), or when selective attention is necessary (e.g., attend right-ear stimuli and ignore left-ear stimuli) (8,13).

The average latency of N1 was 137 ms, substantially longer than the usual 100-ms latency. Because the standard stimuli are sufficiently rapid to be perceived as a sustained stimulus, the frequency change is perceived as a brief alteration in the ongoing stimulus and this may evoke an N1 at a longer latency (22,23). It is also possible that the present N1 wave is a mixture of two different components—the usual N1 response and a mismatch negativity to the frequency change (13).

The P3 amplitude was much larger in the ATTEND than in the IGNORE conditions. This increase in amplitude that occurs when the stimuli are relevant to the subject's task is a characteristic feature of the P3 (8,14). The small P3 in the IGNORE condition may have been caused by the subjects being unable to ignore the targets completely.

Anesthetized Patients

The N1 and P3 waves were present for HITS during preinduction, induction, and recovery, but not during emergence. There were no recognizable waves for MISSES during induction, surgery, and emergence. Our results indicate that auditory endogenous EPs can be recorded in the perianesthetic period. The findings are in contrast with the widespread view that the late EPs are too labile to be useful in the presence of anesthetic agents, even in subanesthetic concentrations (2,3). This view originated from a study that reported that EPs could not be recorded during low-dose cyclopropane anesthesia even though the stimuli were above sensory threshold (24). Donchin and Sutton (25) pointed out that this study had numerous flaws. The major problem was that threshold estimation was not carried out at the same time as the recording of the EPs. When threshold estimation and recording of the EPs were carried out together, there was a good correlation between behavioral performance and the EPs (20,26).

With the exceptions of HITS during emergence and MISSES during recovery, our findings are similar to those recorded with near-threshold stimuli during signal detection tasks in awake subjects: HITS produce N1 and P3 waves, whereas MISSES evoke no recognizable response (20,26).

For MISSES during recovery, however, there seemed to be a small N1 and possibly a very small P3. The *t*-tests performed to determine whether the amplitudes of these waves were different from zero fell short of the $P < 0.01$ criterion for significance. Figure 2 shows a reasonably clear N1 for MISSES during recovery. The discrepancy between the individual measurements and the grand-mean waveforms may, in part, be due to the use of range measurements. When a wave is present, the mean amplitude over a latency range will be less than the peak value. Another possibility is that the analysis of individual measurements included only waveforms based on six epochs or more (to prevent excessive variability), whereas all waveforms were included in the grand-mean waveforms. During recovery, MISSES may therefore have evoked an N1 wave. Squires et al. (20) postulated that the N1 reflects the amount of signal information that is utilized in the decision process and that the P3 represents the certainty of the decision based on that information. The possible presence of an N1 for MISSES might mean that the intensity of the stimuli allowed substantial information transfer, but an impaired decision mechanism prevented detection. It is likely that, despite our repeated instructions, the patients simply forgot the task and ignored the target stimuli. This situation is similar to when the control subjects were asked to read and ignore the stimuli.

Contrary to our expectations, HITS during emergence were not associated with identifiable N1 or P3 waves. Only four patients scored HITS during emergence, and the total number of HITS was only 56, resulting in a low signal-to-noise ratio. Furthermore, the signal acquisition was complicated by numerous artifacts due to movements and shivering. Accordingly, the level of residual noise for HITS during emergence is high. Nevertheless, the N1 and P3 for HITS during emergence are small or absent.

It may be possible for a subject to respond to the target stimuli automatically with little, if any, awareness. Simple auditory detection tasks do not always require full consciousness because they can be performed by subjects who remain in normal stage II sleep (27). The isolated forearm test (28,29) is probably even less satisfactory than signal detection for assessing awareness. With this test, a tourniquet blocks the arterial flow to the forearm, which is thus not affected by neuromuscular blockers. The patient can therefore move the hand to signal "awareness." How to interpret the movements of the hand is a major problem. Patients in a neurovegetative state may open their eyes and move after auditory stimuli. Such automatic behavior must be ruled out before concluding that a simple hand movement by an anesthetized patient is in response to command and reflects awareness.

It is difficult to define consciousness (30). Natsoulas (31) discussed seven different meanings of the word "consciousness." Three are relevant to the present issue. One meaning associates consciousness with normal wakefulness. This is the usual meaning in anesthesiology and neurology (32–34). A second meaning associates consciousness with awareness. Anything may be the object of awareness (e.g., hearing a noise, having a thought). Awareness can be dissociated from wakefulness in both normal subjects and neurological patients. A normal subject can be awake, but unaware of certain aspects of his or her environments. The neurovegetative patient can be awake but totally unaware. A third meaning associates consciousness with self-consciousness. Self-consciousness refers to being aware of one's own perceptions and thoughts. This aspect concerns the ability to think about what one knows or perceives. By contrast, simple awareness is less personal and less reflective. For the rest of the discussion, we shall consider consciousness in this third sense and use the terms wakefulness and awareness for the other two meanings.

The distinctions between consciousness, awareness, and wakefulness have important implications for the problem of unintentional "awareness" during anesthesia (35). There are no specific methods for the on-line detection of intraoperative wakefulness, awareness, or consciousness. Verbal reporting from the patient is currently the only method of establishing that awareness has occurred. For the patient to remember some parts of the surgical procedure probably requires the subject to have been conscious at those times because events that are denied conscious attention are probably not available to intentional forms of remembering (36,37). There may therefore be many instances of wakefulness and awareness during surgery that are not remembered.

Endogenous EPs constitute, in theory, an excellent tool for the detection of unintentional intraoperative awareness or consciousness. Studies in awake controls have repeatedly shown that conscious awareness of a task-relevant stimulus is almost always associated with a P3 provided that the task and recording protocol are adequate (14). The P3 may be used as a communication aid for patients who cannot use their motor system (e.g., "locked-in" patients) (38).

The P3 wave occurs when a subject attends to an unpredictable stimulus. Although the presence of a P3 may indicate that the subject is aware of the stimulus, the absence of the P3 does not indicate an absence of awareness. The stimulus may be predictable or the subject may be attending to something else.

Our main question was whether the link between conscious awareness of a target stimulus and the P3 persisted during the perianesthetic period. Other reports (39–44) have shown the P3 to be attenuated, but still present, at subanesthetic concentrations of anesthetic agents, although no one has studied the P3 in relation to full surgical anesthesia. We found that the link was preserved before anesthesia, despite premedication, during induction, and during recovery. During surgical anesthesia there was no P3, but we do not have a valid behavioral measure because muscle relaxants were used. The link was apparently not valid immediately on emergence from anesthesia, although we do not have sufficient data for definite conclusions. The absence of an N1 and of a P3 may indicate that the detected change did not reach consciousness, despite the motor response. Patients do not usually remember much about what happens during emergence. This may therefore be a period where there is responsiveness but neither clear consciousness nor access to memory.

Our results suggest some possibilities about how consciousness might be monitored during anesthesia. The auditory steady-state response (16) may demonstrate that brainstem-cortical interactions are sufficiently organized to allow consciousness in the sense of wakefulness. They are attenuated during sleep and are not present during surgical anesthesia. The N1 and P3 components of the transient auditory evoked potential may further demonstrate that the subject is conscious of the stimuli in the sense of being aware. During emergence from anesthesia, a subject may be conscious in the sense of being awake, but not conscious in the sense of being aware. One might speculate that the N1 wave reflects simple awareness, whereas the P3 wave reflects full consciousness in the sense of being personally involved in perceiving and remembering the stimulus. The P3 may not only represent access to conscious processing (8,11,12,14,15) but also updating of memory (44,45).

These possibilities, however, remain speculative. Much more research needs to be done. The practical aspects of recording the evoked potentials pose no major difficulty. For future research, it might be better to employ the more usual "oddball" paradigm (14) for P3 recording. The present paradigm was designed to study the P3 and the steady-state responses simultaneously. Different anesthetic agents must be evaluated, and the time-course of recovery of the evoked potentials with each agent must be examined. Much information should come from studying the period of emergence where there are dissociations between different aspects of consciousness.

Adrian Kellett and Dick Mowrey provided essential technical and programming support, respectively. Members of the Royal Victoria Hospital Anaesthesia Department made every effort to provide optimal working conditions. Liam Claffey commented on an earlier version of the manuscript, and Susan Caney provided excellent secretarial assistance.

References

1. Evans JM. Clinical signs and autonomic responses. In: Rosen M, Lunn JN, ed. Consciousness, awareness and pain in general anaesthesia. London: Butterworths, 1987:18–33.
2. Clark DL, Rosner BS. Neurophysiologic effects of general anesthesia: I. The electroencephalogram and sensory evoked responses in man. Anesthesiology 1973;38:564–82.
3. Stockard J, Bickford R. The neurophysiology of anaesthesia. In: Gordon E, ed. A basis and practice of neuroanaesthesia. Amsterdam: North Holland Biomedical Press, 1981:1–46.
4. Hug CC. Lipid solubility, pharmacokinetics, and the EEG: are you better off today than you were four years ago? (editorial). Anesthesiology 1985;62:221–6.
5. Prior PF. The EEG and detection of responsiveness during anaesthesia and coma. In: Rosen M, Lunn M, eds. Consciousness, awareness and pain in general anaesthesia. London: Butterworths, 1987:34–45.
6. Mori K. The EEG and awareness during anaesthesia (editorial). Anaesthesia 1987;42:1153–5.
7. Sharbrough FW. Nonspecific abnormal EEG patterns. In: Niedermeyer E, Da Silva FL, eds. Electroencephalography: basic principles, clinical applications and related fields. Baltimore, Md.: Urban & Schwarzenberg, 1987:163–81.
8. Picton TW, Hillyard SA. Endogenous event-related potentials. In: Picton TW, ed. Human event-related potentials. New York: Elsevier, 1988:361–426.
9. Sebel PS, Heneghan CP, Ingram DA. Evoked responses—a neurophysiological indicator of depth of anaesthesia? (editorial). Br J Anaesth 1985;57:841–2.
10. Jones JG. Use of evoked responses in the EEG to measure depth of anaesthesia. In: Rosen M, Lunn M, eds. Consciousness, awareness and pain in general anaesthesia. London: Butterworths, 1987:99–111.
11. Hillyard SA, Kutas M. Electrophysiology of cognitive processing. Ann Rev Psychol 1983;34:33–61.
12. Hillyard SA, Picton TW. Electrophysiology of cognition. In: Plum F, ed. Handbook of physiology. Section 1. Bethesda, Md.: American Physiological Society, 1987:519–84.
13. Näätänen R, Picton T. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987;24:375–425.
14. Pritchard WS. Psychophysiology of P300. Psychol Bull 1981;89: 506–40.
15. Donchin E, McCarty G, Kutas M, Ritter W. Event-related brain potentials in the study of consciousness. In: Davidson RJ, Schwartz GE, Shapiro D, eds. Consciousness and self-regulation—advances in research and theory. New York: Plenum, 1983:81–121.
16. Plourde G, Picton TW. Human auditory steady-state response during general anesthesia. Anesth Analg 1990;71:460–8.
17. Jasper HH. The ten-twenty electrode system of the International Federation. Electroencephalogr Clin Neurophysiol 1958; 10:371–5.
18. Kirk RE. Experimental design—procedures for the behavioral sciences. 2nd ed. Monterey, Calif.: Brooks/Cole, 1982.
19. Dixon WJ. BMDP statistical software. Los Angeles: University of California Press, 1985.
20. Squires KC, Hillyard SA, Lindsay PH. Vertex potentials evoked during auditory signal detection: relation to decision criteria. Percept Phychophys 1973;14:265–72.
21. Picton TW, Hillyard SA. Human auditory evoked potentials. II. Effects of attention. Electroencephalogr Clin Neurophysiol 1974;36:191–200.
22. Linden RD, Picton TW, Hamel G, Campbell KB. Human auditory steady-state evoked potentials during selective attention. Electroencephalogr Clin Neurophysiol 1987;66:145–59.
23. Mäkelä JP, Hari R, Leinonen L. Magnetic responses of the human auditory cortex to noise/square wave transitions. Electroencephalogr Clin Neurophysiol 1988;69:423–30.
24. Clark DL, Butler RA, Rosner BS. Dissociation of sensation and evoked responses by a general anesthetic in man. J Comp Physiol Psychol 1969;68:315–9.
25. Donchin E, Sutton S. The "psychological significance" of evoked responses: a comment on Clark, Butler, and Rosner. Commun Behav Biol 1970;5:111–4.
26. Hillyard SA, Squires KC, Bauer JW, Lindsay PH. Evoked potential correlates of auditory signal detection. Science 1971; 172:1357–60.
27. Bonnet M. Performance during sleep. In: Webb WB, ed. Biological rhythms, sleep, and performance. New York: John Wiley & Sons, 1982:205–36.
28. Tunstall ME. Detecting wakefulness during general anaesthesia for caesarean section. Br Med J 1977;1:1321.
29. Thornton C, Barrowcliffe MP, Konieczko KM, et al. The auditory evoked response as an indicator of awareness. Br J Anaesth 1989;63:113–5.
30. Allport A. What concept of consciousness? In: Marcel AJ, Bisiach E, eds. Consciousness and contemporary science. New York: Oxford University Press, 1988:160–82.
31. Natsoulas T. Consciousness. Am Psychol 1978;33:906–14.
32. Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia: FA Davis, 1982.
33. White DC. Anaesthesia: a privation of the senses. An historical introduction and some definitions. In: Rosen M, Lunn JN, eds. Consciousness, awareness and pain in general anaesthesia. London: Butterworths, 1987:1–9.
34. Bennett HL. Learning and memory in anaesthesia. In: Rosen M, Lunn JN, eds. Consciousness, awareness and pain in general anaesthesia. London: Butterworths, 1987;132–9.
35. Bitner RL. Awareness during anesthesia. In: Orkin FK, Cooperman LH, eds. Complications in anesthesiology. Toronto: Lippincott, 1983:349–54.
36. Eich E. Memory for unattended events: remembering with and without awareness. Memory Cognition 1984;121:105–11.
37. Tulving E. Memory and consciousness. Can J Psychol 1985;26: 1–12.
38. Farwell LA, Donchin E. Talking off the top of your head: toward a mental prosthesis utilizing event-related potentials. Electroencephalogr Clin Neurophysiol 1988;70:510–23.
39. Adam N. Alteration by enflurane of electrophysiologic correlates of search in short-term memory. Anesthesiology 1979;50: 93–7.

40. Velasco M, Velasco F, Castaneda R, Lee M. Effect of fentanyl and naloxone on the P300 auditory potential. Neuropharmacology 1984;23:931–8.
41. Fowler B, Kelso B, Landolt J, Porlier G. The effects of nitrous oxide on P300 and reaction time. Electroencephalogr Clin Neurophysiol 1988;69:171–8.
42. Estrin WJ, Moore P, Letz R, Wasch HH. The P-300 event-related potential in experimental nitrous oxide exposure. Clin Pharmacol Ther 1988;43:86–90.
43. Samra SK, Bradshaw EG, Pandit SK, Papanicolaou AC, Moore BD. The relation between lorazepam-induced auditory amnesia and auditory evoked potentials. Anesth Analg 1988;67:526–33.
44. Sanquist TF, Rohrbaugh JW, Syndulko KDB, Lindsley DB. Electrocortical signs of levels of processing perceptual analysis and recognition memory. Psychophysiology 1980;17:568–76.
45. Fabiani M, Karis D, Donchin E. P300 and recall in an incidental memory paradigm. Psychophysiology 1986;23:298–308.

Vagal Involvement in the Action of Exogenous Adenosine Triphosphate on Reflex Renal Sympathetic Nerve Activity

Chikuni Taneyama, MD, Hiroshi Goto, MD, Kirk T. Benson, MD, Gregory K. Unruh, MD, and Kasumi Arakawa, MD, PhD

TANEYAMA C, GOTO H, BENSON KT, UNRUH GK, ARAKAWA K. Vagal involvement in the action of exogenous adenosine triphosphate on reflex renal sympathetic nerve activity. Anesth Analg 1991;72:351–8.

The reason why adenine compounds when used as hypotensive agents are devoid of significant reflex sympathetic activity, such as rebound hypertension and tachycardia, is not clearly understood. This study, performed on α-chloralose-anesthetized dogs, examined, first, the effects of adenosine triphosphate (ATP) and adenosine as compared with those of sodium nitroprusside on efferent renal sympathetic nerve activity (RSNA), as an indicator of general reflex sympathetic activity, and second, whether vagal involvement could be demonstrated in the action of ATP and adenosine on RSNA. Renal sympathetic nerve activity increased progressively with increasing doses of sodium nitroprusside (5, 10, and 20 μg/kg) and adenosine (0.5, 2.0, and 4.0 mg/kg), whereas ATP suppressed RSNA at 2.0 and 4.0 mg/kg. High doses of ATP and adenosine (4.0 mg/kg) were injected into intact (n = 7) and vagotomized dogs (n = 7). Both ATP and adenosine induced rapid onset of hypotension without rebound hypertension and tachycardia. After vagotomy, the attenuation of RSNA by ATP was completely abolished and rebound hypertension and tachycardia were observed. Vagotomy did not alter the effect of adenosine on RSNA. It is concluded that ATP-induced hypotension is associated with attenuation of sympathetic efferent nerve activity mediated through vagal afferent pathways. Vagal afferent impulses are thought to be one of the mechanisms that inhibit reflex sympathetic activities, such as rebound hypertension after ATP-induced hypotension. The mechanisms by which adenosine inhibits reflex sympathetic activity are not, however, secondary to vagal afferent involvement and must be multifactorial.

Key Words: ANESTHETIC TECHNIQUES, HYPOTENSIVE—sodium nitroprusside, ATP, adenosine. SYMPATHETIC NERVOUS SYSTEM, SODIUM NITROPRUSSIDE, ATP, ADENOSINE.

Adenosine triphosphate (ATP) and adenosine are endogenous substances with potent vasodilator and negative chronotropic effects. There recently has been a growing interest in ATP and adenosine as effective drugs for controlled hypotension (1–5) and for treatment of supraventricular tachycardia (6,7). Hypotension induced by these compounds is devoid of reflex tachycardia and rebound hypertension caused by activation of the sympathetic nervous system that are typically observed after sodium nitroprusside (SNP)-induced hypotension (1–3). Thus, exogenously administered adenine compounds may attenuate the reflex activation of the sympathetic outflow. In the past, the effects of ATP and adenosine on sympathetic neurotransmission (9–13), and their electrophysiologic effects on the cardiac conduction system (14,15), have been well studied. However, the effects of ATP and adenosine on reflex sympathetic nerve activity have not been clearly established in vivo.

Because parenterally administered ATP is immediately broken down to adenosine by ectoenzymes, it has been assumed that the actions on the cardiovascular system of ATP and adenosine are identical (16,17). However, they may not be identical because vagal involvement can be seen in the action of ATP but not adenosine on the heart (14,15,18).

Questions have been raised whether ATP and adenosine attenuate reflex sympathetic nerve activity and whether the action of ATP on sympathetic nervous system involves a vagal mechanism. The purpose of this study, therefore, was to examine the effects of ATP or adenosine on the reflex sympathetic nerve activity, using direct measurement of renal

---

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from the Department of Anesthesiology, The University of Kansas Medical Center, Kansas City, Kansas. Accepted for publication October 16, 1990.

Address correspondence to Dr. Taneyama, Department of Anesthesiology, The University of Kansas Medical Center, Kansas City, KS 66103.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

sympathetic nerve activity (RSNA), in intact and vagotomized dogs.

Materials and Methods

This study was approved by the Kansas University Institutional Animal Care and Use Committee, and appropriate guidelines for the use of animals were observed during all aspects of this study.

General Preparation

Adult mongrel dogs (15–22 kg) were anesthetized by intravenous thiopental (10 mg/kg) and α-chloralose (100 mg/kg). Additional α-chloralose (20 mg/kg) was administered hourly during the experiment. The dogs were intubated with a cuffed endotracheal tube and ventilated with a Harvard animal ventilator (Millis, Mass.) using oxygen in nitrogen (F_{IO_2}, 0.4) at tidal volumes of 10–15 mL/kg and frequencies of 15–20 cycles/min. Arterial blood gas tensions were measured periodically (model 175 Corning, Boston, Mass.) and were maintained within normal limits (Pa_{CO_2}, 35–45 mm Hg; pH, 7.35–7.45) by adjusting the tidal volume and frequency or by administering sodium bicarbonate. Body temperature was maintained between 37 and 38°C by external warming. The animals were paralyzed with pancuronium (0.1 mg/kg IV) intermittently to avoid artifacts on measurement of sympathetic nerve activity secondary to muscular movement. Polyethylene catheters were placed in the left external jugular vein for measurement of central venous pressure and intravenous administration of agents and in a femoral artery for measurement of arterial pressure. Arterial blood pressure was monitored with a pressure transducer (DTX Spectramed, Oxnard, Calif.) and was recorded continuously. Mean arterial pressure (MAP) was derived by electronic integration of the pulsatile pressure signal.

Recording of Renal Sympathetic Nerve Activity

The left kidney was exposed retroperitoneally by a left flank incision. Renal sympathetic nerves along the renal artery were isolated using a microscope. The distal ends of the strands were crushed and the sympathetic nerves were immersed in mineral oil and placed on a bipolar silver electrode for recording the nerve discharges. The raw nerve signals were amplified by a preamplifier (AVB 10: band width= 50–3000 Hz, Nihon Kohden, Japan). The amplified nerve signals were visualized on a dual-beam oscilloscope (VC 11, Nihon Kohden) and monitored by an audiospeaker. The raw nerve signals were rectified by an absolute value circuit. Integrated renal sympathetic nerve activity (IRSNA) was obtained by integrating the rectified signal with a time constant of 2.0 s using a resistance-capacitance integrator circuit. Because integrated output is dependent on the voltages and frequencies, it was used as a measurement of overall RSNA. Nerve activity was recorded after death in all dogs as a measurement of the level of zero "noise."

Atropine (0.1 mg/kg) was administered to prevent changes in heart rate (HR) by parasympathetic efferent activity. The effectiveness of the cholinergic blockade was tested with a bolus injection of acetylcholine (1 μg/kg) in the preliminary study (19). Atropine has no direct effect on blood pressure.

Data were continuously measured and recorded on a DAT tape PCM recorder (RD-100T, TEAC, Montebello, Calif.) and played back on a multichannel chart recorder (Omnicorder 8M14, Sanei, Japan).

Experimental Protocol

After completion of the surgical preparation, sufficient time (>1 h) was allowed for hemodynamic stabilization before study.

Protocol 1. This protocol measured the dose-response effects of intravenous ATP, adenosine, and SNP on RSNA and HR.

This experiment was performed, using seven mongrel dogs, to determine the dose-response effects of intravenous bolus injection of ATP, adenosine, and SNP on RSNA and HR with respect to the reduction of MAP. Because SNP does not attenuate the baroreflex (20,21), dogs were given SNP first, before receiving either ATP or adenosine, as a control study of reflex RSNA. Sodium nitroprusside was injected in doses of 5 μg/kg (low dose), 10 μg/kg (middle dose), and 20 μg/kg (high dose). Adenosine triphosphate and adenosine were then both injected intravenously in doses of 0.5 mg/kg (low dose), 2.0 mg/kg (middle dose), and 4.0 mg/kg (high dose) with at least 30-min recovery periods between each injection. Each dose of the three agents was found to produce the same level of MAP with the maximum decrease of MAP occurring 20–30 s after each injection in the preliminary study. Renal sympathetic nerve activity and HR were measured with every 10 mm Hg decrement of MAP from the preinjection level (120 ± 10 mm Hg). Renal sympathetic nerve activity was expressed as percentage changes from the resting spontaneous nerve discharge before injection of SNP.

Protocol 2. This protocol measured the effect of vagotomy on time-course changes in RSNA, HR, and MAP after intravenous bolus injection of ATP and adenosine.

This experiment was designed to determine the vagal involvement in the control of RSNA and HR during the injection of ATP and adenosine. Fourteen mongrel dogs were divided into two groups: a neuraxis intact group ($n = 7$) and a cervical bilateral vagotomy group ($n = 7$). After stabilization of RSNA and hemodynamics, ATP and adenosine, 4 mg/kg (high dose), were injected intravenously in the intact and vagotomized dogs. To quantitate RSNA, the resting spontaneous nerve discharge before injection of ATP or adenosine in both groups was defined as 100% control value.

Agents

Adenosine triphosphate-Na_2 (ATP) (116F70802, Sigma) and adenosine (09F0870, Sigma) were dissolved in physiologic saline (20 mg/mL) just before use, employing a stirrer (Bronwill 152, Calif.) with water bath.

Data Analysis

All data were expressed as mean ± SE. Comparisons made within the group were performed using a repeated measurement analysis of variance. Multiple comparisons between individual means were performed using the Newman–Keul's method. Differences with a statistical probability of less than 0.05 were considered to be significant.

Results

Dose-Response Effects of Intravenous ATP, Adenosine, and SNP on RSNA and HR

Mean arterial pressure before SNP, ATP, and adenosine injections was 118 ± 4, 114 ± 3, and 115 ± 4 mm Hg, respectively. Corresponding values of HR were 142 ± 7, 146 ± 5, and 145 ± 8 beats/min. The mean raw values of IRSNA before SNP, ATP, and adenosine injections were 3.1 ± 0.6, 3.3 ± 0.5, and 3.4 ± 0.4 μV, respectively. There were no statistically significant differences in MAP, HR, and RSNA among the three agents.

Dose-response effects of SNP, ATP, and adenosine on RSNA are shown in Figure 1. Sodium nitroprusside and adenosine injections were associated with progressive increases in RSNA in response to decreases in MAP at all three doses. At a MAP reduction of 60 mm Hg with the high dose, the increase in RSNA induced by SNP was significantly greater than that of adenosine ($P < 0.01$). Adenosine triphosphate was associated with progressive increases in RSNA at the low-dose infusion. At the middle and high doses of ATP, RSNA was suppressed dose-dependently.

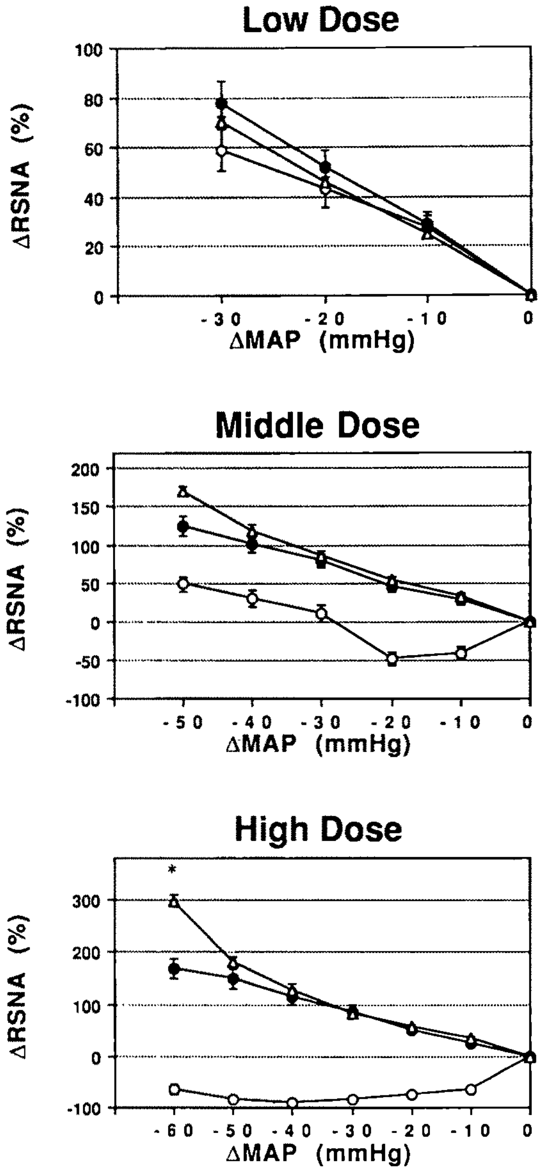


Figure 1. Dose-response effects of intravenous ATP (○), adenosine (●), and SNP (△) on RSNA. Percent increases in RSNA by ATP were significantly less than those associated with middle and high injection doses of adenosine and SNP ($P < 0.01$). *$P < 0.01$: comparison was made only between adenosine and SNP because ATP revealed a baroreflex-independent change in RSNA.

Dose-response effects of SNP, ATP, and adenosine

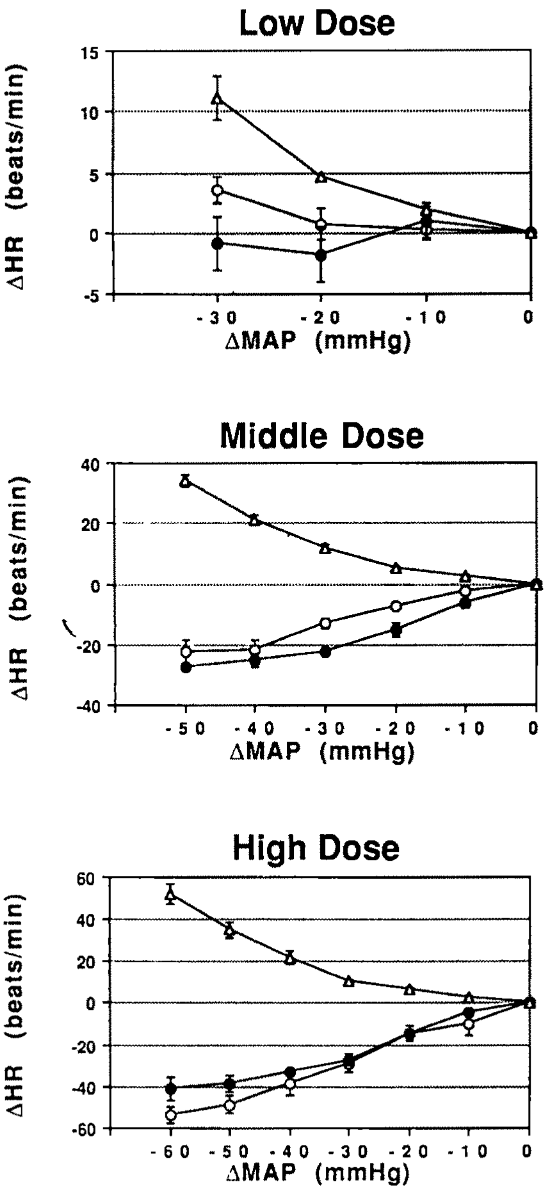


Figure 2. Dose-response effects of intravenous ATP (O), adenosine (●), and SNP (Δ) on HR. Increases in HR with ATP and adenosine were significantly less than those seen with the SNP group in all three doses ($P < 0.01$).

on HR are shown in Figure 2. Heart rate did not change at low doses of ATP and adenosine, but progressively decreased with reduction of MAP at higher doses. Sodium nitroprusside induced dose-dependent increases in HR.

Effect of Vagotomy on Time-Course Changes in RSNA, HR, and MAP During Intravenous Injection of ATP and Adenosine

Baseline levels of MAP, HR, central venous pressure, and RSNA in the intact and vagotomy groups are shown in Table 1. Figure 3 shows one of the actual tracings of the responses of RSNA to intravenous injection of ATP and adenosine in both the intact and vagotomized dogs. Vagotomy completely prevented the ATP-induced suppression of RSNA.

Table 1. Baseline Levels of Mean Arterial Pressure, Heart Rate, Central Venous Pressure, and Renal Sympathetic Nerve Activity in the Intact and Vagotomized Dogs

	Intact group	Vagotomy group
MAP (mm Hg)	118 ± 4	145 ± 2[a]
HR (beats/min)	140 ± 3	178 ± 5[a]
CVP (mm Hg)	3.9 ± 0.3	3.1 ± 0.4
RSNA (%)	100 ± 0	100 ± 0

MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; RSNA, renal sympathetic nerve activity.
Values are expressed as mean ± SE.
[a] Significant difference ($P < 0.05$) between the intact and vagotomy group.

The time-courses of RSNA, HR, and MAP changes in response to ATP (4 mg/kg) injection in the intact and vagotomized groups are shown in Figure 4. Adenosine triphosphate (4 mg/kg) suppressed RSNA in the intact group. This suppression in RSNA induced by ATP was completely abolished by bilateral cervical vagotomy. Heart rate decreased from 140 ± 3 to 83 ± 3 beats/min in the intact group, and from 178 ± 5 to 133 ± 2 beats/min in the vagotomy group. In the vagotomy group, HR significantly increased at between 60 and 150 s after ATP injection.

The maximum decreases in MAP induced by ATP were from 117.9 ± 3.6 to 34.6 ± 1.9 mm Hg in the intact group and from 144.9 ± 1.9 to 76.4 ± 2.4 mm Hg in the vagotomy group. Mean arterial pressure recovered to baseline values 180 s after ATP injection in the intact group. In the vagotomy group, MAP increased above the baseline values at 90 s and remained elevated at 180 s.

The time-courses of RSNA, HR, and MAP changes in response to adenosine (4 mg/kg) injection in the intact and vagotomized groups are shown in Figure 5. In contrast to ATP, adenosine increased RSNA identically in the intact and vagotomy groups. The changes in HR and MAP induced by adenosine did not differ in intact and vagotomized dogs.

Discussion

In the present study, we chose α-chloralose as a basic anesthetic agent because it does not attenuate the arterial baroreflex response (22–24). A relatively small dose of thiopental (10 mg/kg) was administered intravenously but only at the time of induction of

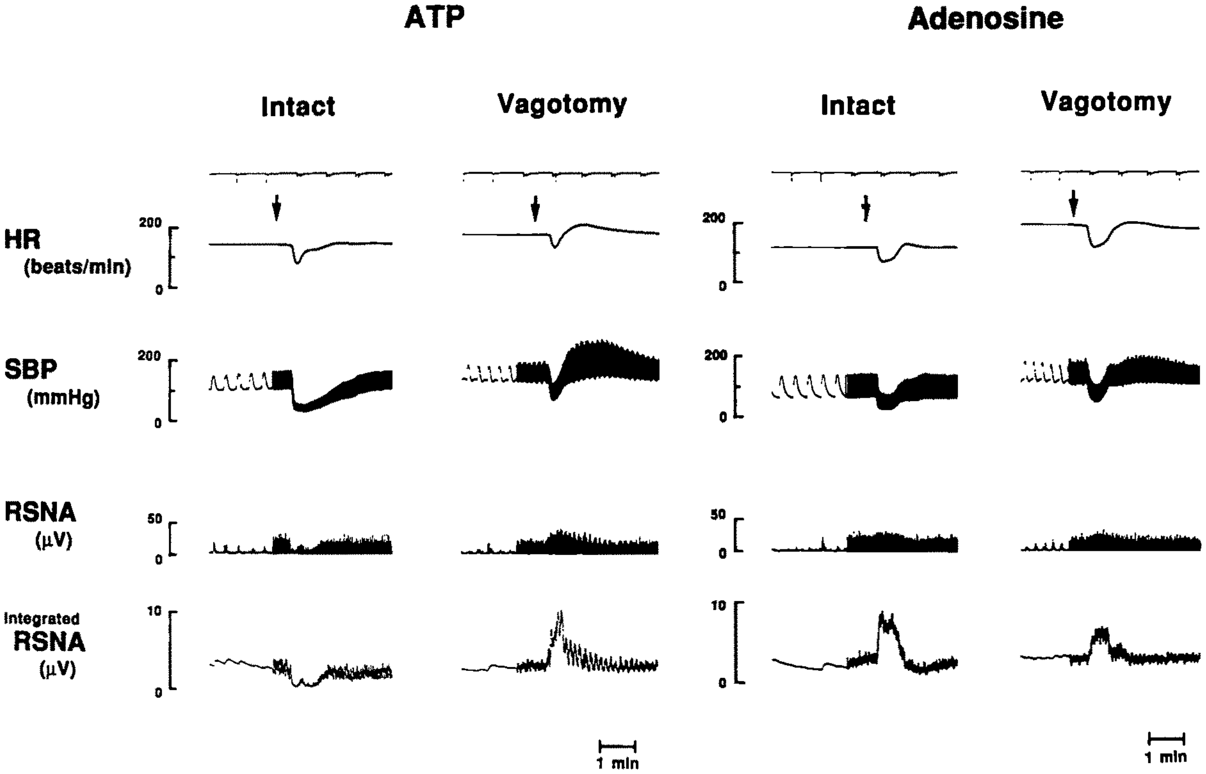


Figure 3. Tracing of the responses of RSNA to intravenous injection of ATP and adenosine in intact and in vagotomized dogs. SBP, systemic blood pressure.

anesthesia. The effect of thiopental on the reflex RSNA, therefore, is thought to be minimal because the study was performed at least 2 h after the induction of anesthesia. This is particularly true because thiopental is an ultra-short-acting barbiturate. The effect of pancuronium on RSNA has not been clearly established. However, we observed that intravenous administration of pancuronium did not affect RSNA at a clinically effective dose (0.1 mg/kg) in the preliminary study.

The present study demonstrated that SNP-induced hypotension was accompanied by a dose-dependent increase in RSNA. This is due, in all likelihood, to a compensatory general reflex sympathetic activation mediated by the arterial baroreceptors. Sodium nitroprusside does not attenuate the arterial baroreflex mechanism involved in increased RSNA in response to arterial hypotension (20,21,25). Small doses of ATP also increased RSNA. However, higher doses of ATP attenuated RSNA. This attenuation was completely abolished by bilateral vagotomy. The effect of vagotomy was due to interruption of vagal afferent, because all animals were given atropine to block vagal efferent pathways. These observations indicate that attenuation of baroreceptor-reflex sympathetic activity involves a vagal afferent mechanism during ATP-induced hypotension.

Additional findings of this study were that rebound hypertension and tachycardia were observed after ATP-induced hypotension in vagotomized but not in intact dogs (Figure 4). Adenosine triphosphate-induced hypotension, generally, is not associated with rebound hypertension and tachycardia in contrast to SNP-induced hypotension (1–3). Rebound hypertension observed during SNP-induced hypotension has been reported to be due to increased plasma catecholamine and renin concentrations (26,27). Because renal sympathetic nerve activity participates in regulation of catecholamine and renin release (28–30), the attenuation of RSNA due to a vagal afferent mechanism may, in part, explain the absence of reflex hypertension and tachycardia during ATP-induced hypotension.

Pelleg et al. (15) and Munoz et al. (18) reported the vagal involvement in the mechanism of action of ATP on the canine cardiac conduction system and concluded that a vagal reflex triggered by ATP could be responsible, at least in part, for ATP-induced bradycardia. Their findings are supported by the present results (Figure 4), which indicate that the changes in HR and MAP induced by high doses of ATP are affected by a vagal afferent mechanism that causes

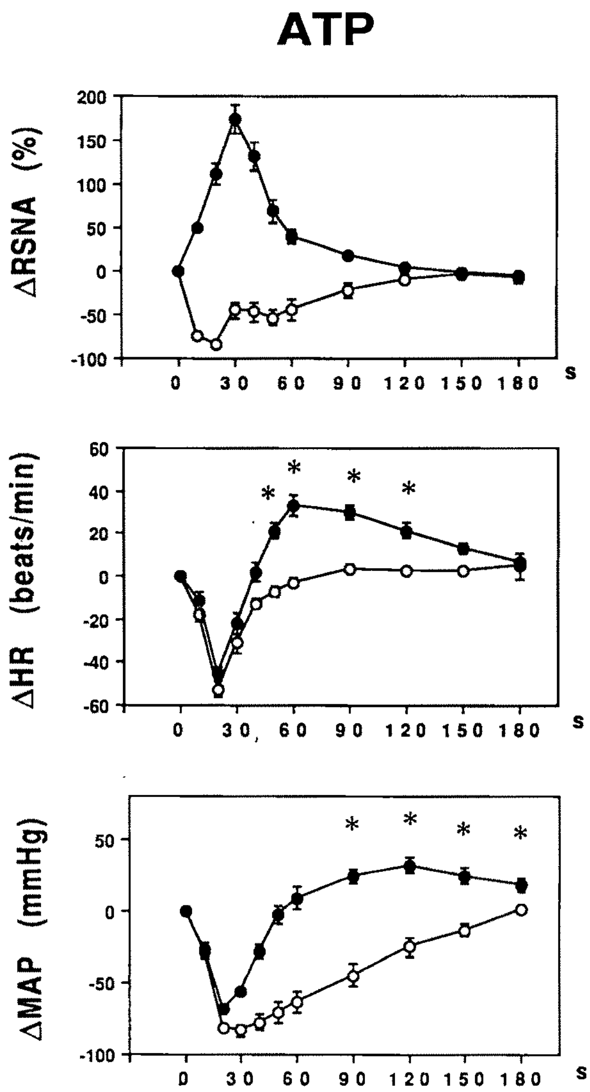


Figure 4. The time-course of changes in RSNA, HR, and MAP in response to ATP (4 mg/kg) injection in intact (○) and in vagotomized (●) dogs. *$P < 0.01$: significantly high above baseline values in within-group comparison for ΔHR and ΔMAP.

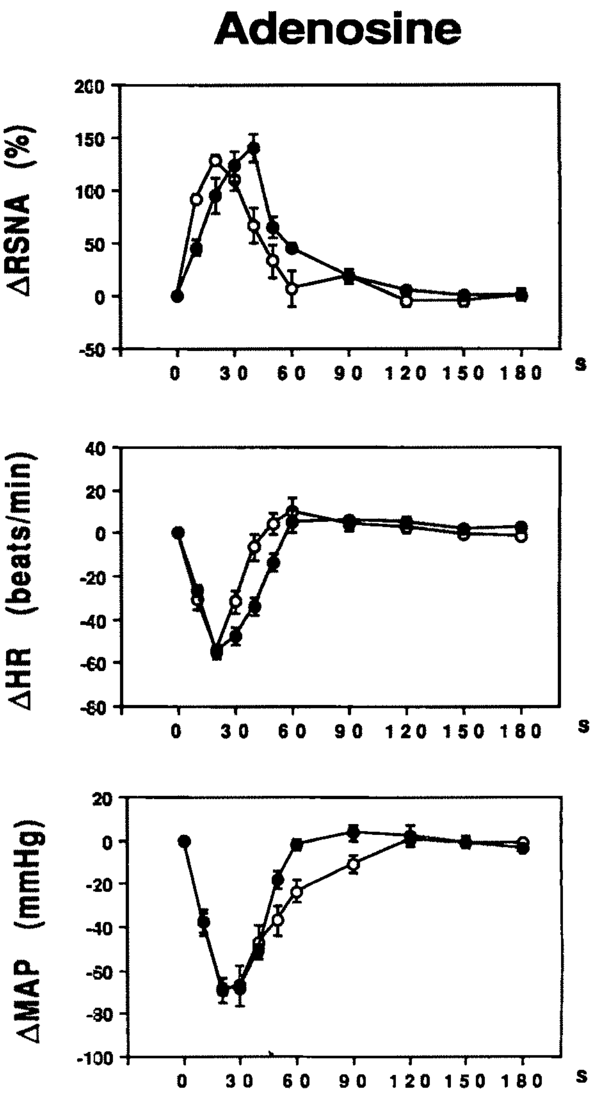


Figure 5. The time-course of changes in RSNA, HR, and MAP in response to adenosine (4 mg/kg) injection in intact (○) and in vagotomized (●) dogs.

suppression of renal efferent sympathetic nerve activity.

Adenosine-induced hypotension is not associated with the reflex tachycardia, rebound hypertension, and increases in plasma catecholamine levels that are seen during ATP-induced hypotension (2,5). Our study showed that adenosine, even in high doses, did not cause rebound hypertension and tachycardia despite the fact that RSNA increased markedly. Additionally, vagal involvement that was confirmed during ATP-induced hypotension was not observed as an action of adenosine. However, the increases in RSNA induced by adenosine were less than those induced by SNP. These findings are in agreement with a report by Delle et al. (8) that increases in RSNA produced by adenosine are less than those produced by SNP. To what mechanisms can one attribute the attenuation of reflex sympathetic response such as reflex tachycardia and reflex hypertension in adenosine-induced hypotension? Hedqvist and Fredholm (10,11) and several other investigators (9,12,13) have reported that adenosine directly inhibits the release of adrenergic neuroeffector transmitters such as norepinephrine in response to sympathetic nerve stimulation in the heart, kidney, and blood vessels. Delle et al. (8) reported that adenosine-induced hypotension is associated with a suppression of postganglionic renal sympathetic nerve activity caused by an inhibition of ganglionic transmission. They believe that their findings may explain why adenosine is devoid of reflex sympathetic activity when it is used for controlled arterial hypotension. Furthermore, it has recently been reported that adenosine suppresses the central nervous system and has anesthetic effects (31). It was speculated that adenosine induces anesthesia by affecting central adrenergic receptors. Even though our study could not explain clearly the mechanisms of attenuation of reflex sympathetic activity by adenosine, we believe that inhibition of adrenergic neurotransmitter release or central nervous system suppression may contribute to attenuation of reflex sympathetic activity.

Adenosine triphosphate and adenosine have been recognized to be almost identical, and they are equipotent on a weight basis (16,17). This is because ATP, when infused parenterally, is rapidly metabolized to adenosine. Sollevi et al. (17) recently reported that ATP administered by the intravenous route is degraded entirely to adenosine and that its cardiovascular effect is dependent on the arterial adenosine concentration. Our study, however, clearly indicates that there is a difference between the effects of ATP and adenosine on RSNA. Rowe et al. (32) also reported that electrophysiologic and cardiovascular hemodynamic effects of ATP are greater than are those of adenosine in dogs. In our study, vagal involvement was demonstrated at least in part in the action of ATP on sympathetic efferent activity and on HR, but it was not found in the action of adenosine. Therefore, the mechanisms of action of ATP and adenosine seem to be clearly different.

In the present study, RSNA and HR were observed only during bolus injections and were not observed during continuous infusion of agents. Although RSNA and HR responses may be less during continuous infusions because of possible baroreflex resetting, we believe that findings derived from the results would be the same.

In conclusion, the present study demonstrates that ATP suppresses reflex sympathetic activity by a vagal afferent mechanism. This is thought to be one of the mechanisms to explain why ATP hypotension is not associated with rebound hypertension or significant catecholamine or renin release. Adenosine does not attenuate reflex RSNA through a vagal afferent mechanism. The reason why adenosine attenuates reflex RSNA may be multifactorial and remains to be elucidated.

The authors thank Dr. Hugh S. Mathewson, Professor of Anesthesiology at The University of Kansas Medical Center, for critical reading of the manuscript.

References

1. Bloor BC, Fukunaga AF, Ma C, et al. Myocardial hemodynamics during induced hypotension: a comparison between sodium nitroprusside and adenosine triphosphate. Anesthesiology 1985;63:517–25.
2. Fukunaga AF, Flacke WE, Bloor BC. Hypotensive effect of adenosine triphosphate compared with sodium nitroprusside. Anesth Analg 1982;61:273–8.
3. Hoffman WE, Satinover ID, Miletich J, Albrecht RF, Gans BJ. Cardiovascular changes during sodium nitroprusside or adenosine triphosphate infusion in the rat. Anesth Analg 1982;61: 99–103.
4. Lagerkranser M, Irestedt L, Sollevi A, Andreen M. Central and splanchnic hemodynamics in the dog controlled hypotension with adenosine. Anesthesiology 1984;60:547–52.
5. Sollevi A, Lagenkranser M, Irestedt L, Gordon E, Lindquist C. Controlled hypotension with adenosine in cerebral aneurysm surgery. Anesthesiology 1984;61:400–5.
6. DiMarco JP, Sellers TD, Berne RM, West A, Belardineli L. Adenosine: electrophysiologic effects and therapeutic use for terminating paroxysmal supraventricular tachycardia. Circulation 1983;68:1254–63.
7. Belhassen B, Pelleg A, Shoshani D, Geva B, Laniad S. Electrophysiologic effects of adenosine-5′ triphosphate, and on atrioventricular reentrant tachycardia. Circulation 1983;68:827–33.
8. Delle M, Ricksten SE, Delbro D. Pre and post ganglionic sympathetic nerve activity during induced hypotension with adenosine or sodium nitroprusside in the anesthetized rats. Anesth Analg 1988;67:307–12.
9. Fredholm BB, Gustavsson LE, Hedqvist P, Sollevi A. Adenosine in the regulation of neurotransmitter release in the peripheral nervous system. In: Berne RM, Rall TW, Rubis R, eds. Regulatory function of adenosine. Boston: Martius Nijhoff, 1983:479–95.
10. Hedqvist P, Fredholm BB. Effects of adenosine on adrenergic neurotransmission: prejunctional inhibition and post junctional enhancement. Naunyn-Schmiedebergs Arch Pharmacol 1976;293:217–23.
11. Hedqvist P, Fredholm BB. Inhibitory effect of adenosine on adrenergic neuroeffector transmission in the rabbit heart. Acta Physiol Scand 1979;105:120–2.
12. Verhaeghe RH, Vanhoutte PM, Shepherd JT. Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenosine nucleotides. Circ Res 1977;40:208–15.
13. Alkadhi KA, Brown TR, Sabouni MH. Inhibitory effect of adenosine on transmission in sympathetic ganglia. Arch Pharmacol 1984;328:16–9.
14. Belhassen B, Pelleg A. Electrophysiologic effects of adenosine triphosphate and adenosine on the mammalian heart: clinical and experimental aspects. J Am Coll Cardiol 1984;4:414–24.
15. Pelleg A, Belhassen B, Terdiman R, Shargorodsky B, Laniado S. Electrophysiological effects of adenosine-triphosphate and adenosine in the canine heart (abstract). Fed Proc 1983;42:731.
16. Olsson RA. Adenosine. In: Drake HAN, Noble MIM, eds. Cardiac metabolism. London: John Wiley & Sons, 1983:527–45.
17. Sollevi A, Lagerkranser M, Andreen M, Irestedt L. Relationship between arterial and venous adenosine levels and vasodilation during ATP- and adenosine-infusion in dogs. Acta Physiol Scand 1984;120:171–6.
18. Munoz A, Sassine A, Carabantes G, Lehujeur C, Koliopoulos N, Puech P. Effects of purinergic compounds on AV conduction: experimental studies in anesthetized dogs. In: Levy S, Gerad R, eds. Recent advances in cardiac arrhythmias. London: John Libbey. 1983:35–8.
19. Zucker IH, Panzenbeck MJ, Barker S, Tan W, Hajdu MA. PGI2 attenuates baroreflex control of renal nerve activity by a vagal

mechanism. Am J Physiol 1988;254(Regul Integrative Comp Physiol 23):R424–30.

20. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45: 340–54.
21. Pickering TG, Gribbin B, Sleight P. Comparison of the reflex heart rate response to rising and falling arterial pressure in man. Cardiovasc Res 1972;6:277–83.
22. Greisheimer EM. The circulatory effects of anesthetics. In: Hamilton WF, ed. Handbook of physiology. Section 2, Volume 3, Circulation. Washington: American Physiology Society, 1965:2477–510.
23. Matsumiya K, Ninomiya I. Anesthetic effects on tonic and reflex renal sympathetic nerve activity in awake cats. Am J Physiol 1989;256:R371–8.
24. Van Citter RL, Franklin DL, Rushmer RF. Left ventricular dynamics in dogs during anesthesia with alpha-chloralose and sodium pentobarbital. Am J Physiol 1964;13:349–54.
25. Taneyama C, Goto H, Goto K, Benson KT, Unruh GK, Arakawa K. Attenuation of arterial baroreflex response to acute hypovolemia during induced hypotension. Anesthesiology 1990;73:433–40.
26. Kinght PR, Lane GA, Hensinger RN, Bolles RS, Bjoraker DG. Catecholamine and renin-angiotension response during hypotensive anesthesia induced by sodium nitroprusside or trimethaphan camsylate. Anesthesiology 1983;59:248–53.
27. Khambatta HJ, Stone JG, Kahn E. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.
28. Dibona, GF. The functions of the renal nerves. Rev Physiol Biochem Pharmacol 1982;94:75–81.
29. Koyama S, Ammous SW, Manning JW. Altered renal vascular tone and plasma renin activity due to fastigial and baroreceptor activation. Am J Physiol 1980;239(Heart Circ Physiol 8): H232–7.
30. Osborn JL, Dibona GF, Thomas HD. B-receptor mediation of renin secretion elicited by low frequency renal nerve stimulation. J Pharmacol Exp Ther 1981;216:265–9.
31. Fukunaga AF, Taniguchi Y, Kikuta Y. Effects of intravenously administrated adenosine and ATP on halothane MAC and its reversal by aminophylline in rabbit (abstract). Anesthesiology 1989;71:A260.
32. Rowe GG, Afonso S, Gurnter HP, et al. The systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine. Am Heart J 1962;64:228–34.

Effects of Fentanyl, Sufentanil, and Alfentanil on Brain Retractor Pressure

Ian A. Herrick, BSc, MD, FRCPC, Adrian W. Gelb, MB, ChB, FRCPC,
Pirjo H. Manninen, MD, FRCPC, Howard Reichman, MD, FRCSC, and
Steven Lownie, MD, FRCSC

HERRICK IA, GELB AW, MANNINEN PH, REICHMAN H, LOWNIE S. Effects of fentanyl, sufentanil, and alfentanil on brain retractor pressure. Anesth Analg 1991;72:359–63.

Sufentanil and alfentanil have been reported to increase cerebral blood flow and intracranial pressure. Agents producing these effects may adversely affect the relationship between brain retractors and underlying cerebral tissues during craniotomy, potentially predisposing the patient to brain retractor injury. The effects of fentanyl, sufentanil, alfentanil, and a placebo (saline) on brain retractor pressure were therefore evaluated prospectively in 24 adults undergoing elective craniotomy. None of these narcotics significantly affected brain retractor pressure. Each significantly and similarly decreased arterial pressure and cerebral perfusion pressure. If these narcotics are administered in doses that avoid adverse hemodynamic changes that could compromise cerebral tissues indirectly, each of the narcotics studied appears safe for intraoperative administration once the cranium is open.

Key Words: ANESTHESIA, NEUROSURGICAL. ANALGESICS, FENTANYL, SUFENTANIL, ALFENTANIL.

Several recent studies in both animals and humans have suggested that sufentanil and alfentanil may be associated with significant increases in cerebral blood flow (CBF) and/or intracranial pressure (ICP) (1–4). The safety of using these agents in neurosurgical patients is thus controversial.

A direct relationship between brain retractor pressure (BRP) and regional cerebral dysfunction has been demonstrated. Brain retractor pressure in excess of 20 mm Hg has been correlated in animals with evidence of reduced regional cerebral cortical blood flow, blood-brain barrier disruption, somatosensory evoked potential abnormalities, and histopathologic evidence of cortical injury (5–9). Once neurosurgical retractors have been placed during craniotomy, agents that alter CBF may change cerebral compliance (via changes in cerebral blood volume [CBV]) and hence the relationship between the retractor and underlying brain parenchyma. This may predispose the patient to brain retractor injury. This study was designed to investigate prospectively the effect of fentanyl, sufentanil, and alfentanil on BRP in a randomized, blinded fashion.

Methods

After institutional review board approval and patient's informed consent were obtained, 24 adult patients scheduled for craniotomy for aneurysm (19 patients), tumor (four), or cerebrospinal fluid leak (one) were studied. Patients were randomized into four groups of six patients each to receive 2.0 μg/kg fentanyl, 0.4 μg/kg sufentanil, 20 μg/kg alfentanil, or normal saline after insertion of the brain retractor. Relative potencies were assigned on the basis of literature reports (3,4,10,11).

General anesthesia was induced using a standardized protocol consisting of preoxygenation, 3.0 μg/kg fentanyl, and 3–5 mg/kg thiopental. Tracheal intubation was facilitated with 1.5 mg/kg succinylcholine after a defasciculating dose of *d*-tubocurarine or atracurium or with atracurium alone (0.5 mg/kg). No premedication was given.

Anesthesia was maintained with isoflurane in air/oxygen and atracurium. Additional thiopental (1–2 mg/kg) was administered as required to control responses to positioning and insertion of skull pins.

Received from the Departments of Anaesthesia and Neurosurgery, University of Western Ontario, University Hospital, London, Ontario, Canada. Accepted for publication October 24, 1990.

Address correspondence to Dr. Herrick, Department of Anaesthesia, University Hospital, London, Ontario, Canada N6A 5A5.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Demographic Data

Study group	Mean age (yr)	Sex		Mean $ETco_2$ (mm Hg)	Mean inspired isoflurane (vol%)	Intracranial compliance	
		M	F			Normal	Abnormal
Fentanyl	55.2 ± 11	1	5	28.3 ± 2.0	0.95 ± 0.31	5	1
Sufentanil	54.5 ± 9	3	3	30.5 ± 3.2	1.00 ± 0.32	4	2
Alfentanil	46.5 ± 14	2	4	28.2 ± 2.7	1.01 ± 0.14	4	2
Normal saline	53.5 ± 6	2	4	30.3 ± 2.5	1.02 ± 0.26	4	2

Values denote mean ± SD.

No additional narcotics were administered before administration of the study drug.

The electrocardiogram, intraarterial blood pressure, oxygen saturation, and end-tidal carbon dioxide ($ETco_2$) were monitored continuously in each patient. Patients were hyperventilated mechanically to maintain $ETco_2$ between 25 and 35 mm Hg, and the inspired isoflurane concentration was established between 0.5 and 1.5 vol% before each study. All patients received 0.5–1.0 g/kg of mannitol intravenously during craniotomy.

After dural opening an Albin–Bunegin pressure-sensitive brain retractor (12), connected to a calibrated Codman pressure monitor, was placed by the surgeon to an initial pressure of approximately 10 mm Hg. All surgical activity was halted, and retractor pressure was monitored for an initial 5-min equilibration period. Output signals from the pressure monitor were amplified and recorded continuously.

After the equilibration period, each patient was given an intravenous bolus of one of the study drugs and the BRP response was monitored continuously for a further 10 min. Each of the study drugs was diluted to 10 mL and administered by an investigator blinded to the drug's identity.

The linearity of the response of the BRP monitor system was tested with fixed loads of 6.5 and 11.7 mm Hg. The system response was found to remain stable within ±0.5 mm Hg for a minimum of 30 min.

Regional cerebral perfusion pressure (rCPP) was calculated according to the formula rCPP = MAP − BRP, where MAP is mean arterial pressure. Statistical comparisons at 1-min intervals were made within each group and between groups for heart rate, MAP, BRP, and rCPP using analysis of variance, for repeated measures where appropriate, and the Student–Newman–Keuls test. Results were considered statistically significant when $P < 0.05$. Assuming a retractor pressure change of 3.5 mm Hg to be clinically significant, the power of this study was estimated to be 95%.

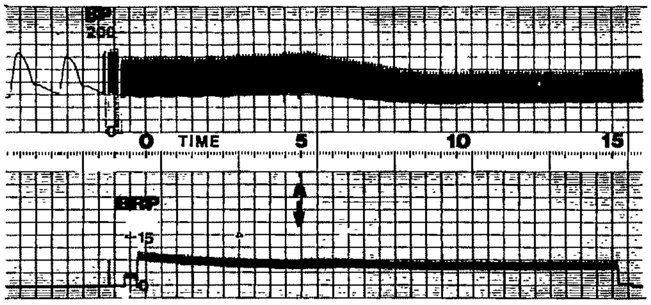


Figure 1. Arterial pressure (BP) (mm Hg) and BRP (mm Hg) as a function of time (min) in a patient in the fentanyl group. *Point A* denotes time of study drug administration.

Results

Patients included 16 women and eight men with a mean age of 52.4 yr (range, 23–70 yr). Study group characteristics were similar (Table 1). Although the sex and age distribution differed somewhat, this would not be expected to affect the results. Patients were categorized on the basis of derangements in intracranial compliance. Patients with aneurysms graded clinically as 0–1 (revised Hunt classification [13]) and those with small tumors without radiographic evidence of brain shift or significant edema were considered to have normal or near normal intracranial compliance. Conversely, patients with grade 2–4 aneurysms and patients with large tumors with radiographic evidence of brain shift or significant associated edema were considered to have decreased intracranial compliance. The distribution of the nine patients with decreased intracranial compliance was similar in each of the study groups.

An example of the recording of arterial pressure and BRP from a patient in the fentanyl group is displayed in Figure 1. Initially, after retractor insertion, BRP declines relatively rapidly as the intracranial contents accommodate the retractor. This process appears to be complete, or nearly complete, within 5 min. Thereafter BRP stabilizes or continues to decline at a much more gradual rate.

Brain retractor pressure demonstrated a gradual decline in all groups after administration of the study

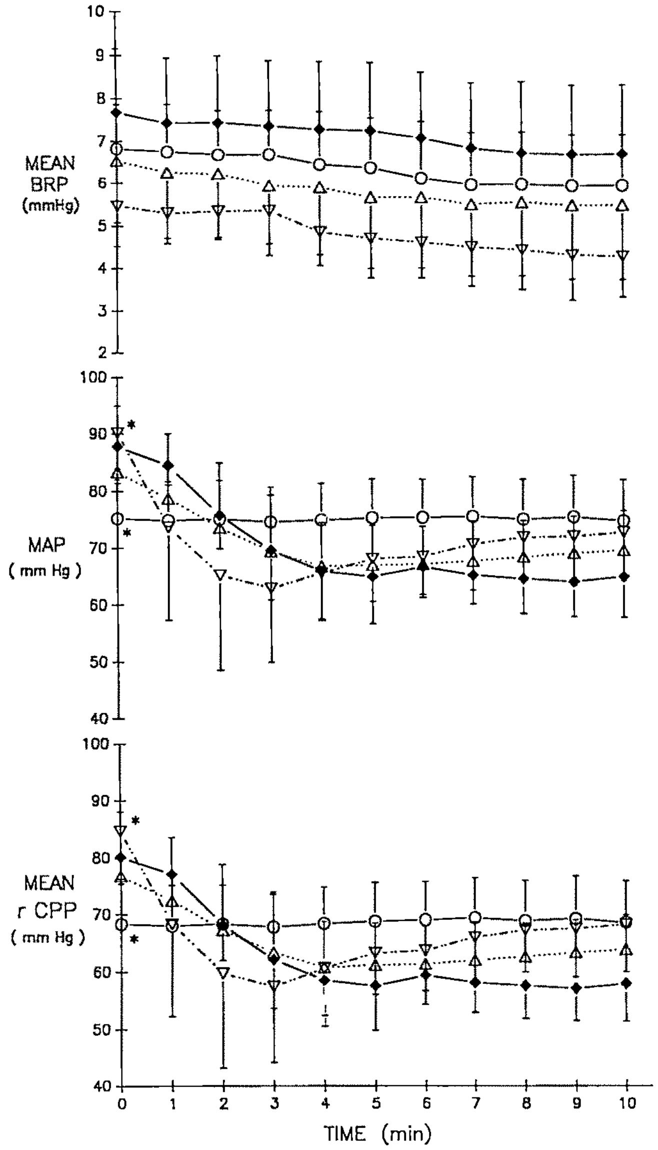


Figure 2. Mean group BRP, MAP, and rCPP (rCPP = MAP − BRP) over time for the fentanyl (△...△), sufentanil (◆——◆), alfentanil (▽—..—▽), and normal saline (○——○) groups. Values were plotted at 1-min intervals after drug administration (time = 0). *Bars* denote SEM. $^*P < 0.05$ between groups.

drug (Figure 2). No statistically significant difference was found between the groups. Within groups the decline in BRP reached significance in the fentanyl and saline groups at 6 min and 7 min and beyond, respectively. The decline in BRP in the sufentanil and alfentanil groups did not reach statistical significance.

Both MAP and rCPP declined markedly in each of the narcotic groups. Within each group the decrease in MAP and rCPP reached statistical significance by 1 min in the alfentanil group and by 2 min in the fentanyl and sufentanil groups. Although each of the narcotic groups demonstrated a decrease in MAP and rCPP, no significant differences were found either between these groups or compared with the saline group, with the exception that MAP and rCPP were significantly higher in the alfentanil group at the time of drug administration compared with the controls (Figure 2).

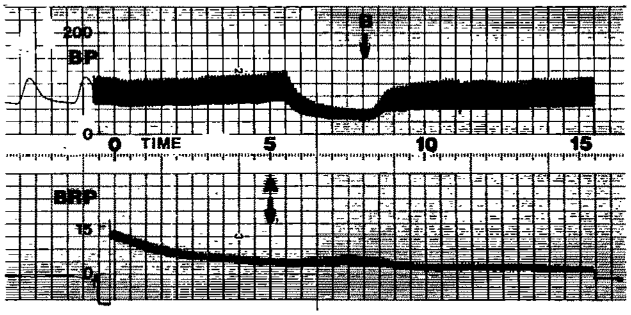


Figure 3. Arterial pressure BP (mm Hg) and BRP (mm Hg) over time (min) in the patient in the alfentanil group who demonstrated an increase in BRP after drug administration. *Point A* denotes time of study drug administration. *Point B* denotes time at which ephedrine (10 mg IV) was given for the marked decrease in MAP.

Heart rate also declined in each of the narcotic groups. Within each group the decrease in heart rate reached statistical significance at 1, 2, and 3 min in the alfentanil, sufentanil, and fentanyl groups, respectively. No significant differences were found between these groups or compared with the control group.

One patient in the alfentanil group had an increase in BRP (1.25 mm Hg) after drug administration (Figure 3). The increase in BRP accompanied a profound decrease in MAP to 36 mm Hg from 79 mm Hg before drug administration. Isoflurane was discontinued and 10 mg intravenous ephedrine was administered to restore the blood pressure. Brain retractor pressure declined as arterial pressure was restored. Central venous pressure at the time of drug administration was 6–7 mm Hg, the inspired isoflurane concentration was 1.0 vol%, and $ETco_2$ was stable at 29 mm Hg. In none of the other patients did retractor pressure increase after administration of the narcotic.

Several patients (in addition to the patient discussed above) required treatment to compensate for hemodynamic changes after study drug administration. Isoflurane was decreased in two patients in the fentanyl group and in three patients in the sufentanil group because MAP decreased to less than 60 mm Hg, and isoflurane was decreased and phenylephrine administered to one patient in the sufentanil group for MAP <55 mm Hg.

Discussion

The results of this study demonstrate that none of the narcotics tested produced significant increases in BRP. The observation period (10 min after drug administration) should have been adequate to detect changes in BRP because previous investigators have demonstrated that the increases in CBF, ICP, and lumbar cerebral spinal fluid pressure occur within this period (1–4). If these effects occur, they would not appear to alter directly the brain retractor-brain parenchyma relationship to any significant degree.

The impact of the narcotics that we studied on CBF and ICP remains controversial. Significant increases in CBF have been reported after the administration of sufentanil to dogs with normal and decreased intracranial compliance (1,2). Small but statistically significant increases in lumbar cerebrospinal fluid pressure have been demonstrated in humans with brain tumors after the administration of sufentanil and alfentanil but not fentanyl (3,4). In contrast, an increase in CBF was not detected after sufentanil administration to patients undergoing coronary artery surgery (14) or healthy volunteers (15). Furthermore, no change in ICP was reported in a group of neurosurgical intensive care unit patients with and without intracranial hypertension after sufentanil administration (16). Several animal studies have also failed to detect adverse changes in CBF and/or ICP after the administration of sufentanil or alfentanil (17–19).

We found administration of each of these narcotics to be associated with decreases in MAP and rCPP. The hemodynamic effects reported in this study parallel the results of other investigators who reported significant increases in ICP despite significant decreases in MAP and rCPP (3). It is thus unlikely that an increase in BRP that might have accompanied drug administration was masked by the decline in MAP and rCPP.

Reduction of regional cortical perfusion has been demonstrated to be an important mechanism in the generation of retractor injury (7–9). Although BRP was not directly affected, the decrease in MAP and rCPP associated with the administration of these narcotics might indirectly compromise cerebral tissue underlying the retractor. The use of these narcotics in neurosurgical anesthesia has been advocated on the basis of their stable hemodynamic profiles; however, the results of this study support the concerns expressed by other investigators regarding the need for careful titration of doses administered intraoperatively to avoid hemodynamic instability (3,18,20).

Maintenance of anesthesia in this study was based on isoflurane in air/oxygen. Although the use of isoflurane may have altered the CBF/ICP response potentially associated with these narcotics, exclusion of maintenance anesthesia was clinically impractical. Changes in CBV and cerebrospinal fluid pressure associated with the use of isoflurane have been reported to stabilize within 30 min after the introduction of this agent (21). Our study was conducted at stable, relatively low, concentrations of isoflurane in moderately hyperventilated patients, conditions that parallel common intraoperative neuroanesthetic conditions and that minimize the impact of isoflurane on CBF, CBV, and ICP. It is also possible that the use of isoflurane contributed to the decline in blood pressure; however, similar hemodynamic changes after narcotic administration have been reported in humans utilizing an anesthetic protocol based on nitrous oxide/oxygen/relaxant (3).

Narcotic dosages in this study were selected to reflect clinically reasonable intraoperative doses. The dosages were considerably smaller than those used in most of the studies that reported increases in CBF and/or ICP. It is possible that these lower doses failed to induce a sufficient increase in CBF to affect retractor pressure. However, the increase in CBF associated with sufentanil was found to be independent of dose, at least in the range from 2 to 200 μg/kg (2).

One patient in the alfentanil group demonstrated a small increase in BRP after drug administration. It is likely that the basis for the observed increase in BRP was the result of a compensatory cerebral vasodilation secondary to the marked decrease in MAP. Although alfentanil administration cannot be implicated as the direct cause of this increase in BRP, this case exemplifies our concern regarding the potential implications of narcotic-induced hemodynamic instability. The marked decrease in arterial pressure that followed alfentanil administration was accompanied by an increase in BRP that could exaggerate the decrease in rCPP and hence the potential for indirect retractor injury. The basis for this profound hemodynamic sensitivity to alfentanil is unclear. The possibility that this effect was associated with a study drug dosage error was investigated and determined to be unlikely. Other factors such as blood pressure, heart rate, central venous pressure, isoflurane concentration, $ETco_2$, and pathology (cerebral aneurysm, grade 0) could not be invoked to explain the observed effect on MAP.

This study was specifically designed to investigate the clinical impact of three narcotics on BRP. An increase in BRP was not observed after their administration, but these results do not necessarily rule out the possibility of increases in CBF, CBV, or ICP. Nevertheless, this study demonstrates that at reasonable intraoperative doses these narcotics do not adversely affect BRP. Provided the narcotics we studied are administered in doses that avoid hemodynamic changes that could potentially compromise rCPP under the retractor, each appears safe for intraoperative use once the cranium is open.

The authors gratefully acknowledge the assistance of Mrs. Kelly Brown in the preparation of this manuscript.

References

1. Milde LN, Milde JH. Cerebral effects of sufentanil in dogs with reduced intracranial compliance (abstract). Anesth Analg 1989; 68:S196.
2. Milde LN, Milde JH, Gallagher WJ. Effects of sufentanil on cerebral circulation and metabolism in dogs. Anesth Analg 1990;70:138–46.
3. Marx W, Shah N, Long C, et al. Sufentanil, alfentanil and fentanyl: impact on cerebrospinal fluid pressure in patients with brain tumors. J Neurosurg Anesth 1989;1:3–7.
4. Jung R, Free K, Shah N, et al. Cerebrospinal fluid pressure in anesthetized patients with brain tumors: impact of fentanyl vs. alfentanil. J Neurosurg Anesth 1989;1:136–7.
5. Albin MS, Bunegin L, Dujovny M, et al. Brain retractor pressure during intracranial procedures. Surg Forum 1975;26: 499–500.
6. Bennett MH, Bunegin L, Albin MS, et al. Evoked potential correlates of graded brain retraction pressure. Stroke 1977;8: 487–92.
7. Albin MS, Bunegin L, Marlin A, Babinski M. Intracranial pressure and regional cerebral blood flow responses to experimental brain retraction pressure. In: Shulman K, Marmarou A, Miller JD, et al., eds. Intracranial pressure. Proceedings of the Fourth International Symposium on Intracranial Pressure. Volume 4. Heidelberg: Springer-Verlag, 1980:131–5.
8. Rosenorn J, Diemer NH. Reduction in regional cerebral blood flow during brain retraction pressure in the rat. J Neurosurg 1982;56:826–9.
9. Rosenorn J, Diemer NH. The risk of cerebral damage during graded brain retractor pressure in the rat. J Neurosurg 1985; 60:608–11.
10. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl and sufentanil in balanced anesthesia. Anesth Analg 1985;64:897–910.
11. Rossow C. Alfentanil. Semin Anesth 1988;7:107–12.
12. Albin MS, Bunegin L, Hensel P. Dimethyl sulfoxide and other therapies in experimental pressure-induced cerebral focal ischemia. Ann NY Acad Sci 1983;411:261–8.
13. Colley PS. Cerebral aneurysm management: anesthetic aspects. In: Cottrell JE, Turndorf H, eds. Anesthesia and neurosurgery. 2nd ed. St. Louis: CV Mosby 1986:411.
14. Murkin JM, Farrar JK, Tweed WA. Sufentanil anaesthesia reduces cerebral blood flow and cerebral oxygen consumption. Can J Anaesth 1988;35:S131.
15. Mayer N, Weinstabl C, Podreka I, Spiss CK. Sufentanil does not increase cerebral blood flow in healthy human volunteers. Anesthesiology 1990;73:240–3.
16. Mayer N, Weinstabl C, Richling B, Czech T, Spiss CK. Impact of sufentanil on intracranial dynamics in neurosurgical ICU patients. Anesthesiology 1989;71:A1138.
17. Bunegin L, Albin MS, Ernst PS, Garcia C. Cerebrovascular responses to sufentanil citrate in primates with and without intracranial hypertension. J Neurosurg Anesth 1989;1:138–9.
18. Lu GP, Gibson JA, Frost EAM, Goldiner PL. Effects of alfentanil vs. sufentanil on brain microcirculation. J Neurosurg Anesth 1989;1:165–6.
19. Lutz LJ, Milde JH, Milde LN. Cerebral effects of alfentanil in dogs with reduced intracranial compliance. J Neurosurg Anesth 1989;1:169–70.
20. Cuillerier DJ, Manninen PH, Gelb AW. Alfentanil, sufentanil and fentanyl: effect on cerebral perfusion pressure (abstract). Anesth Analg 1990;70:S75.
21. Artru AA. Relationship between cerebral blood volume and CSF pressure during anesthesia with isoflurane and fentanyl in dogs. Anesthesiology 1984;80:575–9.

Effects of Succinylcholine on the Pharmacodynamics of Pipecuronium and Pancuronium

Michel Y. Dubois, MD, Neal W. Fleming, MD, PhD, and Dawn E. Lea, RN, BSN

DUBOIS MY, FLEMING NW, LEA DE. Effects of succinylcholine on the pharmacodynamics of pipecuronium and pancuronium. Anesth Analg 1991;72: 364–8.

To study the effects of succinylcholine on subsequent pharmacodynamics of nondepolarizing muscle relaxants, a comparative pharmacodynamic study was carried out in patients having balanced anesthesia (thiopental, fentanyl, nitrous oxide/oxygen) in whom equipotent doses of pipecuronium (80 μg/kg) and pancuronium (100 μg/kg) were given with or without prior administration of succinylcholine (1 mg/kg).

Fifty-two patients were randomly assigned to one of the following four groups: 1, pancuronium (100 μg/kg); 2, pipecuronium (80 μg/kg); 3, succinylcholine (1 mg/kg) plus pancuronium (100 μg/kg); and 4, succinylcholine (1 mg/kg) plus pipecuronium (80 μg/kg). In groups 3 and 4, the nondepolarizing relaxant was given after succinylcholine when the twitch height recovered to 75% of its control value. For maintenance of neuromuscular blockade, additional increments of pancuronium (20 μg/kg) or pipecuronium (15 μg/kg) were given. Neuromuscular function was monitored throughout induction, maintenance, spontaneous recovery, and pharmacologic reversal of the neuromuscular block.

Mean onset times for pancuronium (group 1) and pipecuronium (group 2) given without succinylcholine were (mean ± SEM) 2.5 ± 0.3 and 2.8 ± 0.2 min, respectively. Mean onset times (times to maximum twitch depression) of the two drugs given after succinylcholine (groups 3 and 4) were significantly shorter (1.4 ± 0.4 and 1.6 ± 0.1 min, respectively). Clinical durations (i.e., until 25% twitch recovery of pancuronium and pipecuronium) were not significantly different among the four groups, varying from 81.1 ± 5.4 (group 4) to 107.0 ± 17.0 (group 2) min. Incremental doses used for maintenance of neuromuscular blockade had durations of action ranging from 44.5 ± 5.1 min (group 1) to 52.8 ± 7.3 min (group 3) and were not altered by the prior administration of succinylcholine. After the administration of nondepolarizing relaxant, times for spontaneous recovery of twitch height from 10% to 25% of baseline levels were comparable in all groups (from 15.1 ± 1.7 to 19.8 ± 2.2 min). The response to reversal of residual neuromuscular blockade with neostigmine (2.5 mg) and glycopyrrolate (0.5 mg) was identical in all groups. We conclude that during balanced anesthesia, the use of succinylcholine for intubation does not necessitate subsequent alteration in doses of pancuronium or pipecuronium.

Key Words: NEUROMUSCULAR RELAXANTS, PIPECURONIUM, PANCURONIUM, SUCCINYLCHOLINE. PHARMACODYNAMICS, NEUROMUSCULAR RELAXANTS.

Pipecuronium is a long-acting, nondepolarizing, neuromuscular blocking drug that is slightly more potent than, but similar in structure, onset, duration of action, and recovery to, pancuronium (1–3). However, in contrast to pancuronium, cardiovascular side effects are not observed after administration of pipecuronium either to ASA physical status I or II patients or to patients undergoing coronary artery bypass grafting (4–6).

Long-acting neuromuscular blocking drugs, such as pipecuronium and pancuronium, are commonly used for maintenance of muscle relaxation after succinylcholine given to facilitate endotracheal intubation. Previous studies of the effects of a depolarizing relaxant on the pharmacodynamics of subsequently administered nondepolarizing drugs have produced conflicting results. Katz (7) reported a potentiation of the effects of pancuronium by prior administration of succinylcholine, although subsequent studies by Walts and Rusin failed to demonstrate any interaction (8). Similarly, Chae et al. (9) failed to demonstrate any

---

Supported by a grant from Organon, Inc., West Orange, New Jersey.

Presented in part at the 64th Congress of the International Anesthesia Research Society, Honolulu, Hawaii, March 9–13, 1990.

Received from the Department of Anesthesia, Georgetown University Medical Center, Washington, D.C.; and the Department of Anesthesiology, University of California, Davis, School of Medicine, Davis, California. Accepted for publication October 24, 1990.

Address correspondence to Dr. Dubois, Department of Anesthesia, 3800 Reservoir Road, NW, Washington, DC 20007.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

interaction between succinylcholine and pipecuronium. Their results were, however, derived from a protocol designed to construct a cumulative dose-response curve. Potential interactions between succinylcholine and pipecuronium in a more clinically relevant protocol have not been examined.

The purpose of this study was to ascertain if the pharmacodynamic parameters of equipotent doses of pipecuronium (80 μg/kg) and pancuronium (100 μg/kg) administered during balanced anesthesia were significantly affected by the prior administration of succinylcholine (1 mg/kg) to facilitate endotracheal intubation.

Methods and Materials

After institutional approval, informed consent was obtained from 52 patients who were then enrolled in the study. All patients were ASA physical status I, II, or III between the ages of 22 and 66 yr, had no major organ system disease, and weighed between 47 and 99 kg. Subjects scheduled to undergo surgical procedures with an estimated minimum duration of 2 h were randomly assigned to one of four groups: group 1 (n = 12)—pancuronium, 100 μg/kg alone; group 2 (n = 13)—pipecuronium, 80 μg/kg alone; group 3 (n = 14)—succinylcholine, 1 mg/kg, plus pancuronium, 100 μg/kg; and group 4 (n = 13)—succinylcholine, 1 mg/kg, plus pipecuronium, 80 μg/kg. After premedication with intravenous diazepam (0.15 mg/kg) or midazolam (0.07 mg/kg), anesthesia was induced with thiopental (3–6 mg/kg) and fentanyl (5–10 μg/kg). Anesthesia was maintained using nitrous oxide/oxygen (70%/30%) with supplemental fentanyl and thiopental as necessary. Controlled ventilation maintained end-tidal P_{CO_2} between 35 and 40 mm Hg. Esophageal temperature was maintained between 35 and 37°C by surface warming.

After induction of anesthesia, the isometric force of thumb adduction in response to supramaximal ulnar nerve stimulation was recorded as the "control" value, using a square-wave train-of-four at 2 Hz (0.2 ms duration) every 10 s, for 1 min. Stimulation was via surface electrodes placed over the ulnar nerve at the wrist, and recorded using a force transducer (Myotrace model APM, Professional Instruments, Houston, Tex.). In groups 1 and 2, the nondepolarizing muscle relaxant was then administered over 5 s into the most distal port of a rapidly flowing peripheral intravenous catheter. Intubation of the trachea was attempted within approximately 1 min after the development of the maximal stable neuromuscular blocking effect. When succinylcholine preceded the nondepolarizing drug (groups 3 and 4), intubation was also attempted after development of maximum twitch depression. When T_1 (i.e., first twitch of train-of-four) returned to 75% after succinylcholine administration, the nondepolarizing drug was administered.

After recovery from the initial dose of nondepolarizing drug to the extent that T_1 reached 25% of control, an additional incremental dose of pancuronium (20 μg/kg) or pipecuronium (15 μg/kg) was given to maintain adequate muscle relaxation for the surgical procedure. Patients were allowed to recover spontaneously from their neuromuscular block whenever possible. When T_1 was greater than 25% and the T_4/T_1 ratio was less than 0.75 at the end of surgery, the residual neuromuscular block was reversed with a mixture of 2.5 mg neostigmine and 0.5 mg glycopyrrolate. This was repeated once if necessary.

The following pharmacodynamic parameters were recorded:

Onset time: interval between the injection of the initial dose of pipecuronium or pancuronium and the maximal depression of T_1 (peak effect).

Time to intubation and quality of intubating conditions, determined by the following scale: excellent—jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement; good—jaw relaxed, vocal cords apart and immobile, some diaphragmatic movement; poor—jaw relaxed, vocal cords moving, "bucking"; and inadequate—jaw not relaxed, vocal cords closed.

Clinical duration: interval between the injection of the initial dose or an incremental maintenance dose of pipecuronium or pancuronium and the return of T_1 to 25% of control.

Spontaneous recovery: time required for T_1 to recover from 10% to 25% of control with parallel measurement of T_4/T_1 ratio.

Response to neostigmine: T_1 and T_4/T_1 ratios were recorded for up to 10 min after the administration of reversal drugs.

Hemodynamic parameters: blood pressure and heart rate were recorded before induction of anesthesia, before the initial dose of pancuronium or pipecuronium (after induction) and 2 min after the initial drug administration, before endotracheal intubation, using an automated blood pressure cuff (Dinamap, Critikon, Tampa, Fla.).

Table 1. Neuromuscular Pharmacodynamic Data

	Group 1	Group 2	Group 3	Group 4
Onset (min)	2.5 ± 0.3 (12)	2.8 ± 0.2 (12)	1.4 ± 0.1[a] (13)	1.6 ± 0.1[a] (12)
Intubation (min)	2.7 ± 0.2 (12)	3.3 ± 0.3 (12)	1.7 ± 0.7[a] (13)	1.8 ± 0.7[a] (12)
Clinical duration (min)				
Initial dose	91.2 ± 11.2 (10)	107.0 ± 17.0 (9)	95.3 ± 5.8 (13)	81.1 ± 5.4 (11)
Maintenance dose No. 1	44.5 ± 5.1 (5)	52.8 ± 7.3 (8)	51.7 ± 4.7 (6)	52.0 ± 11.0 (4)
10%–25% recovery (min)	18.4 ± 1.8 (8)	19.6 ± 1.8 (7)	19.8 ± 2.2 (9)	15.1 ± 1.7 (9)
T_1% control				
Before reversal	45.1 ± 11.2 (10)	37.2 ± 5.1 (10)	44.4 ± 9.2 (12)	50.8 ± 6.3 (12)
10 min after reversal	97.5 ± 5.8 (10)	98.7 ± 6.4 (9)	88.6 ± 11.2 (8)	107.9 ± 3.9 (9)
T_4/T_1				
Before reversal	21.9 ± 8.4 (10)	10.2 ± 3.1 (10)	19.4 ± 4.0 (10)	15.3 ± 4.9 (12)
10 min after reversal	74.8 ± 5.0 (10)	72.4 ± 4.0 (9)	64.3 ± 4.4 (8)	78.4 ± 6.4 (9)

Values are expressed as mean ± SEM.
Number of patients is given in parentheses.
Group 1 received pancuronium; group 2, pipecuronium; group 3, succinylcholine and pancuronium; and group 4, succinylcholine and pipecuronium.
[a] Group 3 and 4 values differ from those of groups 1 and 2 in a statistically significant way ($P < 0.05$).

A two-way analysis of variance with interaction using nondepolarizing drugs and the presence or absence of succinylcholine as main factors and two-sample *t*-tests were performed whenever applicable, using the SAS software version 5.18. All reported *P* values are two-tailed. Results of all tests were considered to be statistically significant if the two-tailed *P* value did not exceed 0.05.

Results

There were no significant differences in age, weight, or height between any of these groups. Surgical procedures consisted primarily of abdominal gynecologic and general surgical intestinal operations that lasted an average of 2.9 ± 0.2 h (SEM).

Neuromuscular pharmacodynamic data are summarized in Table 1. There were no statistically significant differences in the maximum effect observed in any of the groups. A complete suppression of T_1 was seen in 49 of 52 patients. Three patients in group 1 had maximum effects of 4%, 6%, and 6% of T_1. Intubating conditions were comparable in all groups. "Good" or "excellent" scores were given to 9 of 12 patients in groups 1 and 2; 3 of 12 patients received a "poor" score in both groups.

Onset Times

Onset times were comparable for pancuronium and pipecuronium administered alone. When succinylcholine was administered to facilitate endotracheal intubation, T_1 recovered to a mean (±SEM) of 78.2% ± 5.4% of control in 12.2 ± 1.5 min before pancuronium administration (group 3), and to a mean of 74.1% ± 1.9% of control in 11.8 ± 1.0 min before the administration of pipecuronium (group 4). Prior administration of succinylcholine produced a statistically significant shortening of the mean onset time for both pancuronium and pipecuronium. There was, however, no statistically significant difference between groups 3 and 4.

Mean intubation times were significantly shorter after the administration of succinylcholine as compared with either pancuronium alone or pipecuronium alone.

Clinical Duration

No significant differences were observed in clinical durations after the initial dose of pancuronium or pipecuronium between groups 1 and 2 or between groups 3 and 4. Mean clinical durations (±SEM) for groups 1 and 3 (pancuronium) were 91.2 ± 11.2 and 95.3 ± 5.8 min, respectively. Mean clinical durations for groups 2 and 4 (pipecuronium) were 107.0 ± 17.0 and 81.1 ± 5.4 min, respectively.

Forty-six patients were given a maintenance dose of either pancuronium or pipecuronium. No significant differences could be found in the clinical duration of either drug.

Recovery

Spontaneous recovery times were similar in all groups. Time for spontaneous recovery of T_1 from 10% to 25% ranged from 15.1 ± 1.7 to 19.8 ± 2.2 min. Prior administration of succinylcholine did not alter the rate of recovery. All groups responded similarly to pharmacologic reversal. At the time of reversal and 10 min after reversal, no difference could be found between groups in either T_1 or T_4/T_1 ratios. Ten minutes after reversal, recovery was adequate (as determined by a T_4/T_1 ratio of >0.75) in 7 of 11 patients in group 1, in 8 of 12 patients in group 2, in 6 of 12 patients in group 3, and in 10 of 12 patients in group 4.

Adverse side effects were limited. An episode of bradycardia in group 2 occurring 2 min after pipecuronium injection was readily treated by atropine. Two patients in group 4 had prolonged neuromuscular blockade. One required 60 min of postoperative ventilatory assistance. No factor known to contribute to prolonged duration of neuromuscular blockade could be found. In the second patient the surgical procedure was shorter than expected, and the clinical duration of the drug exceeded the duration of the surgical procedure.

Discussion

The neuromuscular pharmacodynamic data presented confirm the equipotency of the doses chosen for pancuronium and pipecuronium (i.e., $2 \times ED_{95}$). Onset times, peak effects, and clinical durations were found to be similar for both drugs. Values observed for pancuronium and pipecuronium alone (groups 1 and 2) were comparable to previously reported data in studies using similar doses under balanced anesthesia (2,3,10). An initial 80-μg/kg dose of pipecuronium (group 2) provided a mean onset time of 2.8 ± 0.2 min, consistent production of complete neuromuscular blockade, a mean intubation time of 3.3 ± 0.3 min, and "good" to "excellent" intubation conditions in 75% of cases. This dose of pipecuronium had a mean clinical duration of 107.0 ± 17.0 min, and a mean duration of spontaneous recovery (from $T_1 = 10\%$ to $T_1 = 25\%$) of 19.6 ± 1.8 min. Reversal characteristics of this group were similar to those obtained after pancuronium alone (group 1), especially in reference to the predictability and ease of the pharmacologic reversal.

After the use of succinylcholine (1 mg/kg) for endotracheal intubation, onset times for subsequent doses of both pancuronium and pipecuronium were significantly shorter. This faster onset could be due in part to the study protocol where the nondepolarizing drug was given at a mean $T_1 = 75\%$ recovery from succinylcholine and not at full recovery. It could also reflect the potentiation between depolarizing and nondepolarizing drugs previously reported for other neuromuscular blocking drugs (11–16). There are multiple processes in neuromuscular transmission susceptible to interactions between depolarizing and nondepolarizing drugs including effects on presynaptic receptors (17), postsynaptic receptors (18), and acetylcholinesterase activity (19).

Previous pharmacodynamic studies of drug interaction between succinylcholine and long-acting nondepolarizing agents have produced conflicting results. Katz described a potentiation of both peak effect and clinical duration when pancuronium was given in small doses (20 μg/kg = two-fifths ED_{95}) after full recovery from succinylcholine blockade (7). In a subsequent study by Walts and Rusin, however, using a higher dose of pancuronium (50 μg/kg) and balanced anesthesia (8), no such effect could be found. Similar observations have been made with vecuronium. In small doses (one-half ED_{95}), vecuronium-induced blockade was prolonged by previous administration of succinylcholine (16,20), but with prolonged administration of larger doses of vecuronium there was no evidence of potentiation (13). Also, a small dose of doxacuronium (about one-half ED_{95}) given after full recovery from succinylcholine produced an increased peak effect and duration (14), whereas there was no such potentiation when the full ED_{95} dose was administered (15). Ono et al. studied the pharmacodynamic effects of repeated doses of pancuronium during halothane anesthesia (12) and showed a potentiation of both vecuronium and pancuronium that was time limited: no potentiation could be found after 2 h of administration of the nondepolarizing drug. Our study (which used a $2 \times ED_{95}$ dose of pipecuronium) confirms the finding from Chae et al. (9) (who used $1 \times ED_{95}$). Prior administration of succinylcholine does not appear to affect the clinical duration, the rate of spontaneous recovery, or the pharmacologic reversal of either pancuronium or pipecuronium.

This study protocol intentionally differs from previous studies of succinylcholine interaction. Onset data were calculated from a baseline twitch height of 75% to improve the internal consistency of the results. By administering the nondepolarizing drug at the same level of twitch recovery (i.e., $T_1 = 75\%$), the percentage of receptor occupancy was approximately the same for each patient. In contrast, in other studies when pancuronium was given at a fixed time (i.e., 20–30 min) after the complete recovery of control twitch height, the percentage of receptor occupancy could have varied anywhere from 10% to 80%, consequently increasing the variability of response to the nondepolarizing drug.

Various studies have used different clinical protocols, and final conclusions on potentiation by succinylcholine on subsequent injection of nondepolarizing relaxant are difficult to make between the two classes of muscle relaxants. However, from these and previous results it is possible to suggest that such a potentiation is likely to happen when small doses ($<ED_{95}$) of a nondepolarizing agent are used and when its action lasts less than 2 h.

Cardiovascular effects of these nondepolarizing muscle relaxants were in agreement with previously reported data (1,21–23). Tachycardia was observed in group 1, consistent with the effects of pancuronium. The decrease in blood pressure in group 2, and in heart rate and diastolic blood pressure in group 4, most likely reflects the effects of the induction technique. These changes that occurred with pipecuronium were also found with a "placebo" group and may be attributed to the unopposed cardiovascular effects of the anesthetic technique used (i.e., thiopental and fentanyl) (3). The bradycardia recorded in group 4 may also have been enhanced by the muscarinic effect of succinylcholine because significant change in heart rate was not associated with pipecuronium when administered alone (group 2).

In conclusion, pipecuronium (80 μg/kg) and pancuronium (100 μg/kg) have a comparable neuromuscular pharmacodynamic profile, i.e., similar onset time, peak effect, clinical duration, spontaneous recovery rate, and reversal characteristics. Prior administration of succinylcholine to facilitate endotracheal intubation comparably shortens the onset time of both nondepolarizing drugs but does not modify other pharmacodynamic data. Although we observed characteristic heart rate changes after pancuronium owing to vagolytic/sympathomimetic properties, no clinically significant cardiovascular changes directly related to pipecuronium administration could be elicited. Pipecuronium (80 μg/kg) is well suited for both induction and maintenance of muscle relaxation during balanced anesthesia in surgical procedures lasting at least 90–120 min. Prior use of succinylcholine for intubation does not require adjustment of dose for subsequent administration of pipecuronium.

References

1. Boros M, Szenohradsky J, Marosi GY, Toth I. Comparative clinical study of pipecuronium bromide and pancuronium bromide. Drug Res 1980;30:389–93.
2. Agoston S, Richardson FJ. Pipecuronium bromide (Arduan)—a new long-acting non-depolarizing neuromuscular blocking drug. Clin Anesthesiol 1985;3:361–9.
3. Larijani GE, Bartowski RR, Azad SS, et al. Clinical pharmacology of pipecuronium bromide. Anesth Analg 1989;68:734–9.
4. Barankay A. Circulatory effects of pipecuronium bromide during anaesthesia of patients with severe valvular and ischaemic heart disease. Drug Res 1980;30:386–9.
5. Tassonyi E, Neidhart P, Pittet JF, Morel D, Gemperle M. Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. Anesthesiology 1988;69:793–6.
6. Wierda JMKH, Karliczek GF, Vanderbrom RHG, et al. Pharmacokinetics and cardiovascular dynamics of pipecuronium bromide during coronary artery surgery. Can J Anaesth 1990; 37:183–91.
7. Katz RL. Modification of the action of pancuronium by succinylcholine and halothane. Anesthesiology 1971;35:602–6.
8. Walts LF, Rusin WD. The influence of succinylcholine on the duration of pancuronium neuromuscular blockade. Anesth Analg 1987;56:22–5.
9. Chae SM, Nguyen HD, Nagashima H, Goldiner PL, Duncalf D, Foldes FF. Preliminary administration of succinylcholine does not increase potency and duration of action of pipecuronium (abstract). Anesthesiology 1987;67:A371.
10. Bartkowski R, Larijani GE, Goldberg ME, et al. Onset, duration and reversal of pipecuronium induced neuromuscular blockade under balanced anesthesia (abstract). Anesth Analg 1988;67:58.
11. Katz RL, Norman J, Seed RF, et al. A comparison of the effects of suxamethonium and tubocurare in patients in London and New York. Br J Anaesth 1969;41:1041–7.
12. Ono K. Manabe N, Ohta Y, Morita K, Kosaka F. Influence of suxamethonium on the action of subsequently administered vecuronium or pancuronium. Br J Anaesth 1989;62:324–6.
13. D'Hollander A, Agoston S, Barvais L, Massaut J, Baurain M. Evolution of vecuronium requirements for stable mechanical effect: comparison with or without previous succinylcholine administration. Anesth Analg 1985;64:319–22.
14. Stirt JA, Katz RL, Murray AL, Schehland DL, Lee C. Modification of atracurium blockade by halothane and by suxamethonium. Br J Anaesth 1983;55:S71–5.
15. Katz JA, Fragen RJ, Shanks CA, Dunn K, McNulty B, Rudd GD. The effects of succinylcholine on doxacurium-induced neuromuscular blockade. Anesthesiology 1988;69:604–7.
16. Krieg N, Hendrickx HHL, Crul JF. Influence of suxamethonium on the potency of ORG NC 45 in anaesthetized patients. Br J Anaesth 1981;53:259–61.
17. Baker T, Aguero A, Stanec A, Lowndes HE. Prejunctional effects of vecuronium in the cat. Anesthesiology 1986;65:480–4.
18. Waud BE, Waud DR. Interaction among agents that block endplate depolarization competitively. Anesthesiology 1985;63:4–15.
19. Simon G, Biro K, Karpati E, Tuba Z. The effect of the steroid muscle relaxant pipecuronium bromide on the acetylcholinesterase activity of red blood cells in vitro. Drug Res 1980;30: 350–3.
20. D'Hollander AA, Agoston S, DeVille A, Cuvelier F. Clinical and pharmacological actions of a bolus injection of suxamethonium: two phenomena of distinct duration. Br J Anaesth 1983;53:131–4.
21. Seltzer JL, Bartowski RR, Azad SS, et al. Cardiovascular effects of pipecuronium bromide under balanced anesthesia (abstract). Anesth Analg 1988;67:S266.
22. Foldes FF, Nagashima H, Nguyen HD, Weiss R, Goldiner PL. The human cumulative dose-response of pipecuronium bromide under balanced anesthesia (abstract). Anesthesiology 1986;65:A116.
23. Wierda JMKH, Richardson FJ, Agoston S. Dose-response relation and time course of action of pipecuronium bromide in humans anesthetized with nitrous oxide and isoflurane, halothane, or droperidol and fentanyl. Anesth Analg 1989;68: 208–13.

ANESTH ANALG 1991;72:369–76

Effect of Ranitidine on Bupivacaine Disposition

Wayne T. Brashear, PhD, Kathy J. Zuspan, MD, Noam Lazebnik, MD,
Betty R. Kuhnert, PhD, and Leon I. Mann, MD

BRASHEAR WT, ZUSPAN KJ, LAZEBNIK N, KUHNERT BR, MANN LI. Effect of ranitidine on bupivacaine disposition. Anesth Analg 1991;72:369–76.

This study was undertaken to determine the effect, if any, of ranitidine on bupivacaine disposition in 28 women undergoing cesarean section. Before epidural anesthesia, ranitidine (50 mg IM) or sodium citrate (30 mL orally) was administered to groups of 14 parturients each. Ranitidine was administered 2 h before epidural anesthesia and sodium citrate was administered 10 min before the epidural. Maternal plasma samples were collected after epidural anesthesia with bupivacaine. A total of 15 maternal plasma samples were taken from the time of administration of epidural anesthesia up to 180 min. Postpartum plasma and urine samples were also collected from both mothers and neonates. Plasma samples were collected up to 48 h postpartum at intervals of 12, 24, and 48 h. Urine samples were collected at six 6-h intervals up to 36 h postpartum. A two-way analysis of variance with repeated measures demonstrated that there was no significant difference in bupivacaine levels between the maternal plasma curves of the ranitidine and the control groups. At the time of delivery, plasma levels of bupivacaine and its N-dealkylated metabolite PPX (2,6-pipecolylxylidine) were no different in the mothers or neonates of either group. There was no significant difference in plasma protein binding of bupivacaine in the presence of ranitidine. The excretion rates of bupivacaine and PPX were not measurably influenced by ranitidine. The amount of bupivacaine excreted. the amount of metabolite excreted, and the percentage of drug excreted as metabolite in maternal urine were not significantly different. These data indicate that there is no measurable effect of ranitidine on the disposition of bupivacaine in parturients.

Key Words: ANESTHESIA, OBSTETRICAL—ranitidine-bupivacaine interaction. ANESTHETICS, LOCAL—bupivacaine. HISTAMINE, RANITIDINE—bupivacaine interaction.

The potential for drug interactions exists with H_2-antagonists because they are frequently administered concomitantly with other drugs. Ranitidine is an H_2-antagonist that may be used for preoperative prophylaxis of aspiration pneumonitis. The literature on drug interactions involving ranitidine interactions is extensive (1,2). However, very few of these studies have investigated interactions of H_2-antagonists during pregnancy. Wilson et al. reported that a 150-mg oral dose of ranitidine influences the disposition of bupivacaine (3). Their study used a preoperative dose of ranitidine (150 mg) that was associated with significantly higher plasma levels of bupivacaine. The findings of Wilson indicate that the use of preoperative ranitidine results in higher levels of bupivacaine. The purpose of our study was to investigate the effect of a smaller (50 mg intramuscular [IM]) preoperative dose of ranitidine on the disposition of bupivacaine used for epidural anesthesia.

The interest in potential drug interactions of ranitidine has been stimulated by the finding that a similar drug, cimetidine (an H_2-antagonist), influences the metabolism of many drugs that undergo oxidative metabolism (2). This has been supported by the observation that cimetidine binds to cytochrome P450 and inhibits the hepatic microsomal mixed function oxidase system (4). The effect of H_2-antagonists on hepatic blood flow has also been of interest because histamine is known to dilate mesenteric arteries through H_1- and H_2-receptors (5). Some reports have indicated that hepatic blood flow may be reduced by cimetidine (6). In addition to this, cimetidine has been shown to affect the kidney's active

---

Supported in part by U.S. Public Health Service Grant MOI-RR00210 through the Perinatal Clinical Research Center, MetroHealth Medical Center, and Case Western Reserve University, Cleveland, Ohio.

Received from the Departments of Obstetrics and Gynecology, and Anesthesiology, MetroHealth Medical Center, Cleveland; and the Perinatal Clinical Research Center, Case Western Reserve University, Cleveland, Ohio. Accepted for publication October 30, 1990.

Address correspondence to Dr. Brashear, Mantech Environmental Technology, Inc., P.O. Box 31009, Dayton, OH 45431-0009.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

transport system for organic cations by competing with basic drugs for tubular secretion (7).

In general, the interactive effects of ranitidine are less than those of cimetidine. Although both drugs are H_2-antagonists, their chemical structures are different. A major structural difference between these drugs is that ranitidine has a furan ring and cimetidine has an imidazole ring. This may account for ranitidine's lower binding affinity to cytochrome P450 and negligible effect on cytochrome P450-mediated oxidative metabolism (8). Like cimetidine, ranitidine can influence the renal clearance of drugs (9). However, due to the fact that therapeutic levels of ranitidine are only about 25% of those of cimetidine, the effect of ranitidine upon renal clearance may not be significant (10).

Materials and Methods

Twenty-eight women and their infants were studied during cesarean section and after delivery. All of the women had elective cesarean sections, underwent epidural anesthesia using 0.5% bupivacaine, and delivered healthy term infants. Student's *t*-test was used to compare patient characteristics; dichotomous variables were evaluated by χ^2 analysis. Preoperatively, 14 study patients were given ranitidine (50 mg IM) 2 h before cesarean section. Control patients received sodium citrate (30 mL) 10 min preoperatively. The study was approved by the Human Investigation Committee of MetroHealth Medical Center; informed consent was obtained from each patient before enrollment in the study.

Maternal plasma samples were collected at timed intervals as previously described (11). At the time of delivery, maternal vein, cord vein, and cord artery samples were collected. After delivery, plasma samples were collected from mothers and infants at 12, 24, and 48 h. Urine was collected from both mothers and neonates over six 6-h intervals starting from the time of delivery. Samples were refrigerated while being collected and frozen at −20°C. Not all samples could be collected from all patients.

The plasma levels of bupivacaine and its pharmacologically inactive metabolite 2,6-pipecolylxylidine (PPX) were measured by gas chromatography/mass spectrometry (GC/MS) (11). Maternal plasma levels of bupivacaine in the control and ranitidine groups were analyzed by a two-way analysis of variance with repeated measures. This was performed on the plasma levels of bupivacaine from the administration of the drug to 48 h postpartum. The areas under the plasma curves (AUC) were determined by a combination of trapezoidal and log trapezoidal methods (12), and the AUC values were corrected for dosage. The area following the last observation was estimated by dividing the final value by the elimination rate constant. The maternal elimination rate constant was measured from the time of delivery through 48 h postpartum. The neonatal elimination rate constant was measured from the cord artery sample through 48 h postpartum. The elimination half-life ($t_{1/2}$) was calculated as ln(2)/k. Other pharmacokinetic parameters measured were the maximum maternal plasma concentration (C_{max}) and the corresponding time (t_{max}). Student's *t*-test was used to compare the AUC, $t_{1/2}$, C_{max}, and t_{max} values.

Maternal and neonatal samples obtained at the time of delivery were analyzed for bupivacaine and PPX. The bupivacaine and PPX levels of the ranitidine and control groups were compared by Student's *t*-test. The cord vein versus maternal vein and the cord artery versus cord vein ratios of bupivacaine and PPX were also compared in this manner. Student's *t*-test was used to compare the bupivacaine levels and the half-life values for neonatal plasma.

The amounts of bupivacaine and PPX excreted in maternal and neonatal urine were measured by GC/MS (11). A two-way analysis of variance with repeated measures was used to compare these values in maternal urine collected over six 6-h intervals. In maternal urine, the total amounts of bupivacaine and PPX, the percentages of metabolite, and the percentages of the total dose excreted were compared by Student's *t*-test. Linear plots of the maternal and neonatal ratios of PPX to total drug described urinary excretion. A two-way analysis of variance with repeated measures compared the maternal ratios. In neonatal urine, the ratios of PPX to the total drug excreted (over six 6-h collection intervals) were analyzed by Student's *t*-test.

Protein binding of bupivacaine was measured in maternal plasma from 16 parturients before the administration of any medication. The binding experiments were carried out at bupivacaine concentrations of 1.0 μg/mL. Equilibrium dialysis incubations were performed at 37°C using plasma diluted 1:10 with buffer (0.08 M Na_2HPO_4, 0.03 M NaH_2PO_4, 0.6% wt/vol NaCl [pH 7.4]) and at ranitidine concentrations of 0.0, 0.5, and 0.05 μg/mL as previously described (13). Paired *t*-tests were used to evaluate the protein binding data.

Statistical significance was accepted at $P < 0.05$. One-tailed, paired *t*-tests were used to analyze the protein binding data, with statistical significance accepted at $P < 0.05$. Using the precision of the bupivacaine plasma assay, power analysis (14) indicated

Table 1. Maternal Characteristics of Study Group

Maternal characteristic	Control (n = 14)	Ranitidine (n = 14)	Significance level
Age (yr)	28 ± 4[a]	27 ± 5	NS
Parity	(22–37)	(19–34)	
Nulliparous	1	3	NS[b]
Multiparous	13	11	
Delivery			
Repeat section	11	10	NS[b]
Primary section	3	4	
Indication for section			
Elective	14	12	NS[b]
Other	0	2	
Intrapartum anesthesia	163 ± 43	164 ± 40	NS
0.5% Bupivacaine (mg)	(100–235)	(75–215)	
Anesthesia to delivery	48 ± 18	50 ± 8	NS
interval (min)	(25–100)	(39–67)	
Complications			
>200 lb	2	7	
Gestational diabetes	1	0	
Weight (lb)	174 ± 37	207 ± 47	NS
	(147–289)	(136–300)	

NS, not significant.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

[b] By the χ^2-test.

that 14 patients per group are needed to reduce the probability of a type II error to 0.1 ($\Delta = 0.1\bar{X}$). Parameters tested by Student's t-test were also checked using the Mann–Whitney test statistic. Statistical analysis was performed using BMDP statistical software (BMDP Statistical Software, Los Angeles, Calif.).

Results

Patient Characteristics

Ranitidine was administered 125 ± 37 min (range, 50–166) preoperatively. The ranitidine-to-delivery interval was 152 ± 39 min (range, 88–248). Patient characteristics are shown in Tables 1 and 2. Comparison of the maternal study groups (Table 1) shows that two of the ranitidine patients were not scheduled for elective cesarean sections. One patient presented in labor with a history of a previous section for a failed induction. The other patient had a history of a previous cesarean section and presented with late decelerations and mild contractions. The inclusion or exclusion of these patients did not significantly influence the characteristics of the study groups. The neonatal characteristics, shown in Table 2, indicate that the infants from these groups are similar with respect to gestational age, birth weight, and Apgar scores. One infant from the control group was acidotic, having a cord artery pH value of 7.15. The inclusion or exclusion of this infant did not significantly influence the characteristics of the neonatal groups or the outcome variables related to neonatal drug disposition.

Plasma Disposition

The maternal plasma levels of bupivacaine after epidural anesthesia are shown in Figure 1. A two-way analysis of variance with repeated measures indicated that there is no significant difference between the ranitidine or control groups from the time of the administration of the bupivacaine to 48 h postpartum ($F[1,11] = 0.03$, $P = 0.86$). Separate analysis of the plasma curves before and after the time of delivery did not show a significant difference. Other pharmacokinetic parameters were also evaluated. These data, shown in Table 3, indicate that there is no significant difference in the AUC (corrected for dose), $t_{1/2}$, C_{max}, or t_{max} for either group. Some of the pharmacokinetic parameters suggested that a small treatment effect may be present. This was evidenced by a longer $t_{1/2}$, a larger AUC, a higher C_{max}, and a longer t_{max} for the ranitidine group. However, none of these differences were statistically significant. It may be that an effect, attributable to ranitidine, may be hidden by intersubject variability. The standard deviations for the pharmacokinetic parameters in

Table 2. Characteristics of Neonates

Neonatal characteristic	Control (n = 14)	Ranitidine (n = 14)	Significance level
Gestational age (wk)	39 ± 1[a] (37–42)	40 ± 1 (38–42)	NS
Birth weight (g)	3305 ± 528 (2520–4310)	3424 ± 352 (2795–4080)	NS
Apgar < 7			
1 Min	1	0	
5 Min	0	0	
Cord venous pH	7.35 ± 0.05 (7.22–7.40)	7.34 ± 0.03 (7.28–7.39)	NS
Cord artery pH	7.29 ± 0.06 (7.15–7.37)	7.27 ± 0.03 (7.20–7.34)	NS
Complications			
Large for gestational age	1	0	
Polyhydramnios	1	0	
Hyperbilirubinemia	0	1	
Heart murmur	1	1	

NS, not significant.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

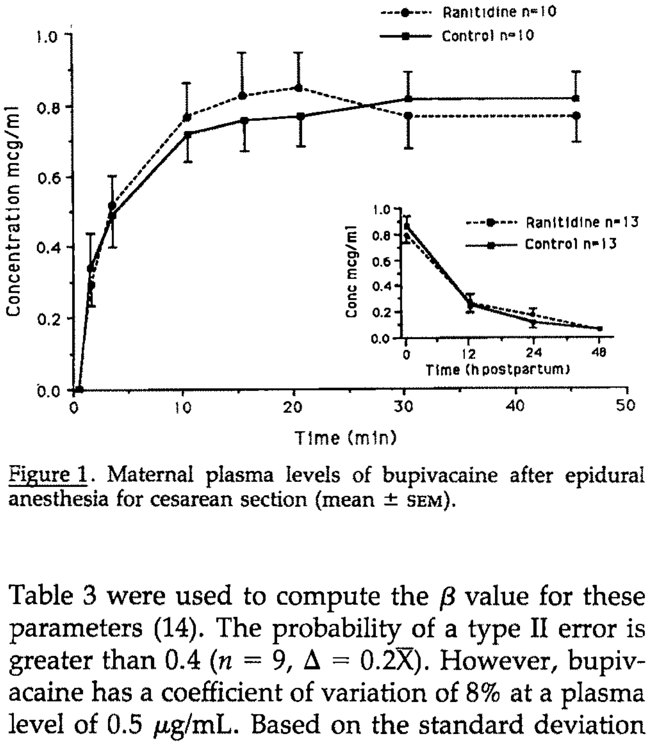


Figure 1. Maternal plasma levels of bupivacaine after epidural anesthesia for cesarean section (mean ± SEM).

Table 3 were used to compute the β value for these parameters (14). The probability of a type II error is greater than 0.4 (n = 9, $\Delta = 0.2\overline{X}$). However, bupivacaine has a coefficient of variation of 8% at a plasma level of 0.5 μg/mL. Based on the standard deviation of the assay, the probability of a type II error is less than 0.1 (n = 9 and $\Delta = 0.2\overline{X}$).

Samples obtained at the time of delivery (153 ± 39 min after the administration of ranitidine) were analyzed for levels of bupivacaine and PPX. The results, shown in Table 4, indicate that there are no significant differences in the drug or metabolite levels of the maternal delivery sample, cord vein, or cord artery. Ratios of the drug and metabolite in the delivery samples indicate that these are not affected by preoperative exposure to ranitidine (Table 5). The neonatal half-life of bupivacaine and the neonatal bupivacaine levels at 12, 24, and 48 h postpartum also were not significantly different (Table 6).

Urinary Disposition

The data in Table 7 describe the maternal urinary disposition of bupivacaine and PPX. The amounts of bupivacaine and PPX excreted in maternal urine over 36 h did not differ significantly between the control and ranitidine groups. The percentage of metabolite to the total urinary excretion and the percentage of the administered dose excreted were not significantly different. Figure 2 shows the maternal ratio of PPX to the total amount of drug excreted broken down into six 6-h intervals. A two-way analysis of variance with repeated measures indicated that the control and ranitidine groups did not differ significantly (F[1,14] = 3.01, P = 0.10). The amounts of bupivacaine and PPX in maternal urine were also analyzed using a two-way analysis of variance with repeated measures. Again, the groups did not differ significantly over the six 6-h collection intervals ($P > 0.05$).

The neonatal ratio of PPX to the total urinary excretion is similar in the control and ranitidine groups as shown in Figure 3. Analysis of the neonatal ratios by Student's t-test indicated that there is no significant difference between the control and ranitidine groups.

Protein Binding

Plasma protein binding was not affected by the presence of ranitidine. At a concentration of 1.0 μg/mL,

Table 3. Pharmacokinetic Parameters

	Control (n = 9)	Ranitidine (n = 9)	Significance level
Maternal $t_{1/2}$ (h)	7.12 ± 1.50[a] (3.95–8.99)	7.25 ± 1.41 (5.33–9.53)	NS
AUC[b] (h/L)	0.0462 ± 0.0114 (0.0322–0.0704)	0.0502 ± 0.0154 (0.0163–0.0654)	NS
C_{max} (μg/mL)	1.03 ± 0.32 (0.62–1.66)	1.13 ± 0.31 (0.77–1.70)	NS
t_{max} (min)	49 ± 24 (15–90)	54 ± 27 (15–90)	NS

NS, not significant.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

[b] Dose-corrected: AUC = AUC_{actual}/dose.

Table 4. Bupivacaine and 2,6-Pipecolylxylidine Levels at Delivery in Control and in Ranitidine-Treated Parturients

	Control (n = 13)	Ranitidine (n = 13)	Significance level
Bupivacaine (ng/mL)			
Maternal vein	748 ± 307[a] (96–1300)	731 ± 259 (285–1103)	NS
Cord vein	272 ± 285 (90–1181)	219 ± 98 (35–441)	NS
Cord artery	155 ± 156[b] (37–583)	113 ± 37[c] (62–151)	NS
PPX (ng/mL)			
Maternal vein	17 ± 18 (0–48)	14 ± 19 (0–51)	NS
Cord vein	15 ± 14 (0–44)	18 ± 15 (0–44)	NS

NS, not significant; PPX, 2,6-pipecolylxylidine.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

[b] n = 10.

[c] n = 5.

bupivacaine was 98.53% protein-bound. In the presence of ranitidine at 0.5 and 0.05 μg/mL, bupivacaine protein binding was 98.50% and 98.53%, respectively. Paired t-test demonstrated no significant difference.

Discussion

The purpose of this study was to determine whether a single dose of ranitidine alters the disposition of bupivacaine used for epidural anesthesia in obstetric patients. The study evaluated pharmacokinetic parameters in both mothers and infants. None of the maternal or neonatal parameters studied indicated a significant difference between the control and the ranitidine groups. The data indicated that 50 mg of IM ranitidine does not alter the metabolism, placental transfer, or protein binding of bupivacaine. Some of the pharmacokinetic parameters suggested that a small treatment effect may be present. This was evidenced by a longer $t_{1/2}$, a larger AUC, a bigger C_{max}, and a longer t_{max} for the ranitidine group. However, none of these differences was statistically significant.

The results of our study are in contrast to a previous study by Wilson et al., which measured bupivacaine levels in parturients who received a 150-mg oral dose of ranitidine 2 h before epidural anesthesia (3). The study in which 150 mg oral ranitidine was given found that parturients pretreated with ranitidine (n = 9) had higher mean plasma levels of bupivacaine than the control group (n = 7), which did not receive ranitidine. This occurred only at 40 min after the administration of epidural anesthesia ($P < 0.05$). However, there was no statistically significant difference in plasma levels of bupivacaine in blood samples obtained at the time of delivery and at other time intervals. The study of Wilson also used a smaller sample size than the present study.

A dose of 150 mg of orally administered ranitidine

Table 5. Cord Vein/Maternal Vein and Cord Artery/Cord Vein Ratios in Control and Ranitidine-Treated Parturients

	Control (n = 12)	Ranitidine (n = 13)	Significance level
Bupivacaine			
Cord vein/maternal vein	0.36 ± 0.40[a] (0.14–1.57)	0.32 ± 0.17 (0.12–0.71)	NS
Cord artery/cord vein	0.61 ± 0.36[b] (0.12–1.48)	0.87 ± 0.52[c] (0.43–1.77)	NS
PPX			
Cord vein/maternal vein	0.86 ± 0.33[d] (0.40–1.43)	1.64 ± 1.43[e] (0.67–4.29)	NS

NS, not significant; PPX, 2,6-Pipecolylxylidine.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

[b] $n = 10$.

[c] $n = 5$.

[d] $n = 9$.

[e] $n = 6$.

Table 6. Bupivacaine Levels (ng/mL) in Neonatal Plasma at Various Times After Delivery and Half-Life Calculated From Plasma Data

	Control (n = 13)	Ranitidine (n = 13)	Significance level
12 h	17 ± 7[a] (4–25)	22 ± 17 (0–62)	NS
24 h	7 ± 4 (0–13)	9 ± 7 (0–21)	NS
48 h	0 ± 0 (0–0)	1 ± 2 (0–7)	NS
Neonatal $t_{1/2}$ (h)	5.11 ± 0.56[b] (4.53–6.22)	5.46 ± 1.58[b] (4.52–9.53)	NS

NS, not significant.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

[b] $n = 9$.

Table 7. Bupivacaine and 2,6-Pipecolylxylidine Excretion by Control and Ranitidine-Treated Parturients

	Control (n = 7)	Ranitidine (n = 11)	Significance level
Total bupivacaine excreted (mg/mL)	0.41 ± 0.17[a] (0.23–0.68)	0.76 ± 0.53 (0.29–2.08)	NS
Total PPX excreted (mg/mL)	15.81 ± 10.27 (5.53–35.86)	19.70 ± 12.97 (3.30–41.05)	NS
Percentage of metabolite to total product excreted	97 ± 1 (95–99)	96 ± 21 (92–98)	NS
Percentage of total dose excreted	11 ± 8 (4–26)	17 ± 14 (3–48)	NS

NS, not significant; PPX, 2,6-Pipecolylxylidine.

[a] Value is expressed as mean ± SD, with the range given in parentheses.

has a bioavailability of 53% ± 14% (15). Because Wilson et al. used an oral dose of 150 mg, they used a larger pharmacologic dose of ranitidine than the 50 mg IM dose used for our study. This may be responsible for the statistically significant difference in the plasma levels of bupivacaine. The study of Morichau-Beauchant et al. (15) compared 50 mg intravenous and 150 mg oral ranitidine administration. In normal patients an oral dose of 150 mg produced an AUC value of 1.88 ± 0.45 $\text{mg}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$, whereas a 50-mg intravenous dose gave an AUC value of 1.22 ± 0.20 $\text{mg}\cdot\text{L}^{-1}\cdot\text{h}^{-1}$ (15). This is a statistically significant

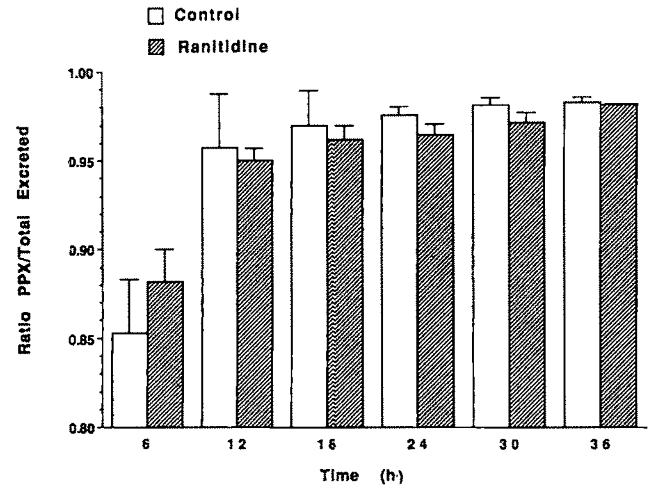


Figure 2. Maternal ratio of PPX, a metabolic product of bupivacaine, to total products (PPX plus unchanged bupivacaine) excreted by ranitidine-treated and control patients (mean ± SEM).

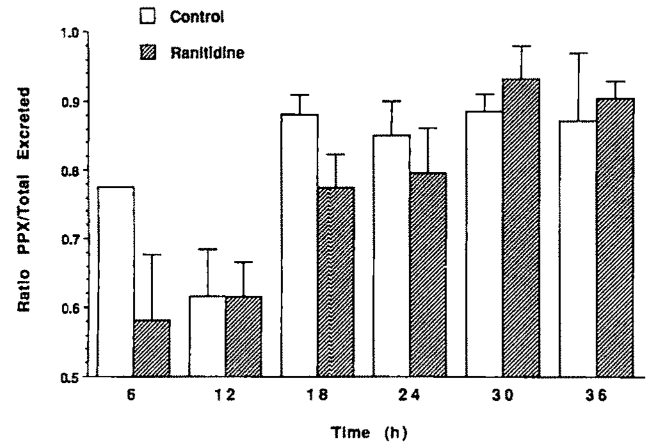


Figure 3. Neonatal ratio of PPX, a metabolic product of bupivacaine, to total products (PPX plus unchanged bupivacaine) excreted by ranitidine-treated and control infants (mean ± SEM).

difference ($P < 0.05$), which suggests that patients in the study of Wilson et al. had a higher level of ranitidine exposure.

Patients in Wilson's study were given oral ranitidine 2 h before epidural anesthesia. It has been reported that a 150-mg oral dose of ranitidine has a t_{max} of 150 ± 79 min and a C_{max} of 380 ± 146 ng/mL (15). Because these patients were dosed 2 h before the epidural they were probably close to the peak concentration of 380 ng/mL 40 min after epidural anesthesia. In contrast, a 50-mg intravenous dose has a plasma concentration less than 20 ng/mL after 2.5 h (15). Therefore, 2.5 h after the administration of a 50-mg IM dose, the plasma concentration of ranitidine is most probably less than the plasma concentration from a 150-mg oral dose. Thus, the findings of Wilson et al. may be attributed to a larger dose and higher plasma levels of ranitidine.

It may be that a small effect, attributable to ranitidine, may be hidden by intersubject variability. The β value for the pharmacokinetic parameters shown in Table 3 is greater than 0.4. This indicates that the number of patients used for this study may be inadequate to completely exclude the possibility of a type II error, and thus, the findings should be interpreted accordingly. This is in contrast to a β value less than 0.1 calculated from the precision of the bupivacaine plasma assay ($n = 9$, $\Delta = 0.2\overline{X}$). It is estimated that 50 patients per group (14) would be needed to obtain a β value of 0.1 with study patients ($\Delta = 0.2\overline{X}$). However, even though a statistically significant difference might be found with a larger sample size, the data suggest that any difference would probably not be clinically significant.

Clinical studies have shown that preoperative ranitidine offers effective protection against acid aspiration during anesthesia (16). A 50-mg IM dose of ranitidine increased the gastric pH above 2.5 in about 94% of the patients studied and decreased the gastric volume to less than 25 mL in 92% of the patients (16). Other studies indicate that on an equimolar basis ranitidine is about four times more potent than cimetidine (17). Our study has found no statistically significant drug interaction attributable to ranitidine. Therefore, the intramuscular administration of ranitidine may be a safe and effective means of prophylaxis for aspiration pneumonitis during cesarean section.

The authors would like to express appreciation to Dr. B. Kuhnert, Wyeth Pharmaceuticals, Inc., Philadelphia, Pa., who initiated this study, and to Dr. N. Lazebnik, MetroHealth Medical Center, Cleveland, Ohio, for his assistance with the clinical aspects of this study. Appreciation is also expressed to Sue Fitz, RN, and to the staff of the Perinatal Clinical Research Center at Cleveland Metropolitan General Hospital for their help in obtaining clinical samples.

References

1. Mitchard M, Harris A, Mullinger BM. Ranitidine drug interactions—a literature review. Pharmacol Ther 1987;32:293–325.
2. Smith SR, Kendall MJ. Ranitidine versus cimetidine, a comparison of their potential to cause clinically important drug interactions. Clin Pharmacokinet 1988;15:44–56.
3. Wilson CM, Moore J, Ghaly RG, Mclean E, Dundee JW. Plasma bupivacaine concentrations associated with extradural anaesthesia for caesarean section: influence of pretreatment with ranitidine. Br J Anaesth 1986;58:1330–1.
4. Pelkonen O, Puurunen J. The effect of cimetidine on in vitro and in vivo microsomal drug metabolism in the rat. Biochem Pharmacol 1980;29:3075–80.

5. Wieslaw P, Jague LL, Tepperman BL, Miller TA, Jacobson ED. Histamine H_1 and H_2 receptor vasodilation of canine intestinal circulation. Am J Physiol 1977;233:E219–24.
6. Feely J, Wilkinson GR, Wood AJ. Reduction of liver blood flow and propranolol metabolism by cimetidine. N Engl J Med 1981;304:692–5.
7. Somagyi AA. New insights into the renal secretion of drugs. Trends Pharmacol Sci 1987;8:354–7.
8. Rendic S, Kajfez F, Ruff HH. Characterization of cimetidine, ranitidine, and related structures. Interaction with cytochrome P-450. Drug Metab Dispos 1983;11:137–42.
9. Muirhead M, Bochner F, Somagyi A. Pharmacokinetic drug interactions between triamterene and ranitidine in humans: alteration in renal and hepatic clearances and gastrointestinal absorption. J Pharmacol Exp Ther 1988;244:734–9.
10. Rodvold KA, Paloucek FP, Jung D, Gallastegui J. Interaction of steady-state procainamide with H_2-receptor antagonists cimetidine and ranitidine. Ther Drug Monit 1987;9:378–83.
11. Kuhnert PM, Kuhnert BM, Stitts JM, Gross TL. The use of a selected ion monitoring technique to study the disposition of bupivacaine in mother, fetus, and neonate following epidural anesthesia for cesarean section. Anesthesiology 1981;55:611–7.
12. Yeh KC, Kwan KC. A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and spline approximation. J Pharmacokinet Biopharm 1978;6:79–98.
13. Kuhnert BR, Zuspan KJ, Kuhnert PM, Syracuse CD, Brashear WT, Brown DE. Lack of influence of cimetidine on bupivacaine levels during parturition. Anesth Analg 1987;66:986–90.
14. Stolley PD, Strom RL. Sample size calculations for clinical pharmacology studies. Clin Pharmacol Ther 1986;39:489–90.
15. Morichau-Beauchant M, Houin G, Mavier P, Alexandre C, Dhumeaux D. Pharmacokinetics and bioavailability of ranitidine in normal and cirrhotic patients. Dig Dis Sci 1986;31: 113–8.
16. Williams JG, Strunin L. Pre-operative intramuscular ranitidine and cimetidine. Anaesthesia 1985;40:242–5.
17. Lebert PA, Mahon WA, MacLeod SM, et al. Ranitidine kinetics and dynamics. II. Intravenous dose studies and comparison with cimetidine. Clin Pharmacol Ther 1981;30:545–50.

Effect of Fentanyl and Nitrous Oxide on the Desflurane Anesthetic Requirement

Ahmed F. Ghouri and Paul F. White, PhD, MD

GHOURI AF, WHITE PF. Effect of fentanyl and nitrous oxide on the desflurane anesthetic requirement. Anesth Analg 1991;72:377–81.

The minimum alveolar anesthetic concentration (MAC) of desflurane (I-653) was determined when administered with 60% nitrous oxide (N_2O) in oxygen after a standardized induction sequence consisting of 0, 3, 6, or 9 μg/kg intravenous (IV) fentanyl followed by 3–6 mg/kg IV thiopental and 1.5 mg/kg IV succinylcholine. For comparison, we also determined the isoflurane MAC with 60% N_2O in oxygen after an induction dose of 3 μg/kg IV fentanyl and similar doses of thiopental and succinylcholine. All patients were undergoing elective surgical procedures. The minimum alveolar anesthetic concentration in patients given isoflurane and 60% N_2O with 3 μg/kg fentanyl was 0.4%, approximately 20% below previously reported MAC values for isoflurane with 60% N_2O alone. The minimum alveolar anesthetic concentration of desflurane with 60% N_2O plus 0, 3, 6, and 9 μg/kg IV fentanyl was 3.7%, 3.0%, 1.2%, and 0.1%, respectively. Thus, the MAC-lowering effect of 3 μg/kg IV fentanyl appears to be similar with both isoflurane and desflurane. Fentanyl, 3–9 μg/kg IV, produces dose-dependent decreases in the MAC of desflurane.

Key Words: ANALGESICS, OPIOID—fentanyl. ANESTHETICS, GASES—nitrous oxide. ANESTHETICS, VOLATILE—desflurane. POTENCY, ANESTHETIC—MAC.

Desflurane (I-653), a new volatile anesthetic, is a halogenated methyl ethyl ether that differs from isoflurane by the substitution of a fluorine for a chlorine at the α-ethyl position (1). Although the minimum alveolar anesthetic concentration (MAC) of desflurane alone and in combination with nitrous oxide has been determined in humans (2), it will likely be used in combination with other anesthetic adjuvants. Therefore, it is important to understand the interaction between desflurane and intravenous (IV) anesthetic, analgesic, and muscle relaxant drugs that are commonly used during general anesthesia.

This study was designed to determine the effect of varying doses of fentanyl on the desflurane anesthetic requirement when administered in combination with thiopental and nitrous oxide (N_2O).

Materials and Methods

Ninety-three healthy, ASA physical status I and II adult patients scheduled for elective surgical procedures were randomly assigned to one of five study groups according to a protocol that was approved by the Washington University Human Studies Committee. Written informed consent was obtained from each patient. Patients in group 1 received 3 μg/kg fentanyl with isoflurane and 60% N_2O in oxygen (O_2). Patients in groups 2–5 received 0, 3, 6, or 9 μg/kg IV fentanyl, respectively, together with desflurane and 60% N_2O in O_2. Patients were excluded from participation in the study if they were women of childbearing potential, anemic (hematocrit < 30%), hypothermic, or had a history of coronary artery disease, preexisting lung disease, or unusual reactions to centrally active sedative or analgesic medications. Also excluded were patients who chronically used drugs known to affect the volatile anesthetic requirement, or those who had had general anesthesia within 7 days before surgery.

All subjects fasted for a minimum of 12 h before their scheduled surgery. Routine intraoperative monitoring included electrocardiogram, noninvasive measurement of blood pressure (Dinamap, Critikon, Tampa, Fla.), and hemoglobin O_2 saturation

---

Supported by a grant from Anaquest, Inc. to the Division of Clinical Research in the Department of Anesthesiology at Washington University.

Received from the Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri. Accepted for publication November 6, 1990.

Address correspondence to Dr. White, Department of Anesthesiology, Washington University School of Medicine, Box 8054, 660 South Euclid Avenue, St. Louis, MO 63110.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

(Ohmeda Biox 3700, Pleasanton, Calif.), a precordial stethoscope, neuromuscular blockade monitor (Relaxograph, Puritan Bennett, Tewksbury, Mass.), and an esophageal temperature probe. The inspired and end-tidal concentrations of N_2O, isoflurane, desflurane, and carbon dioxide were measured using an infrared gas analyzer (Datex, Puritan Bennett). The monitor was calibrated before each surgical procedure using gases analyzed to ±0.01% accuracy (Scott Medical Products, Plumsteadville, Pa.). Intraoperative variables were recorded at 1-min intervals until 5 min after surgical (skin) incision. Subsequent measurements were performed at 5-min intervals until the end of surgery.

Patients received no premedication before arriving in the operating room. After obtaining baseline measurements, a defasciculating dose of 2–3 mg IV *d*-tubocurarine was administered to each patient. Those randomized to groups receiving fentanyl (1 and 3–5) were given 3–9 μg/kg IV over 2–5 min immediately before induction of anesthesia. Thiopental, 3–6 mg/kg IV, was given at the time of induction to produce loss of the eyelash reflex. Succinylcholine, 1.5 mg/kg IV, was administered to facilitate intubation. After intubation, anesthesia was maintained using 60% N_2O in O_2, and a predetermined concentration of volatile agent until the time of incision. The end-tidal anesthetic gas concentration was kept constant for at least 15 min before skin incision to allow for adequate equilibration. Recovery of succinylcholine-induced neuromuscular blockade was confirmed at the time of incision by a return of the Relaxograph tracing to within 5% of the presuccinylcholine baseline value in all patients.

Minimum alveolar anesthetic concentration was determined by recording the presence or absence of movement, as adopted from Eger et al. (3). We considered movement to be an "all-or-none" phenomena in response to skin incision. Breath-holding, bucking, and coughing were not considered to be movement. Minimum alveolar anesthetic concentration was determined for each treatment group using Dixon's up-down method, an oscillatory technique commonly used in estimating ED_{50} and LD_{50} values for events that are characterized by a quantal response (4).

The initial alveolar concentrations of the volatile agents in groups 1–5 were 1% isoflurane and 7%, 6%, 5%, and 4% desflurane, respectively. If a patient moved during skin incision, the next study patient (within the same treatment group) received a higher concentration of the volatile agent. Conversely, if the patient did not move, the next patient in that particular group received a lower concentration of the agent. An attempt was made to keep the increments in which the concentration of the volatile agent was increased or decreased constant (increment equivalent to approximately 10% of the concentration administered to the first patient in each treatment group). Minimum alveolar anesthetic concentration in the presence of N_2O was determined from an analysis of the percentage of patients in each treatment group moving at various end-tidal concentrations (5) and was defined to be the alveolar concentration preventing 50% of patients from moving in response to skin incision.

If movement occurred, 25–100 mg IV thiopental and 1–2 mg IV vecuronium were administered to ensure an adequate depth of surgical anesthesia and to prevent further movement. After incision, anesthesia was maintained using 60% N_2O in O_2 and 0.5%–1.0% isoflurane (group 1) or 60% N_2O in O_2 and 1.5%–6% desflurane (groups 2–5). Vecuronium, 1–2 mg IV bolus doses, were administered as needed to maintain an adequate degree of neuromuscular blockade throughout the operation. Ventilation was adjusted to maintain a $P_{ET}CO_2$ of 30–40 mm Hg as measured by the gas analyzer, and the temperature was maintained at 35.0°–37.5°C for the duration of the surgical procedure using heated, humidified gases and fluid warmers.

Statistical analysis was performed using the FASTAT data analysis system (Systat, Inc., Evanston, Ill.). Continuous variables were analyzed using a one-way analysis of variance or the Student's *t*-test when appropriate. Descriptive variables were analyzed using χ^2 analysis or Fisher's exact test. Data are reported as mean values ± SD. *P* values < 0.05 were considered statistically significant.

Results

All study groups (1–5) were comparable with respect to demographic data (Table 1). There were no statistically significant differences between treatment groups with respect to age, weight, height, sex, race, ASA physical status, or types of surgical procedure (e.g., orthopedic, gynecologic). Intraoperative data from all experiments are also summarized in Table 1. There were also no significant differences between groups with regard to duration of surgery, temperature at the time of incision, or the time elapsed from induction until incision. As expected, the two high-dose fentanyl groups required significantly less thiopental for induction of anesthesia than the group receiving no fentanyl. Hemodynamic changes during induction were similar in all five treatment groups.

Table 1. Demographic Data in the Five Groups of Patients.

	Patient groups				
	1	2	3	4	5
n	21	18	17	20	17
Sex (M/F)	7/14	9/9	9/8	7/13	7/10
Age (yr)	40 ± 14	40 ± 12	44 ± 11	44 ± 10	39 ± 13
Weight (kg)	74 ± 16	78 ± 19	83 ± 16	82 ± 21	80 ± 20
Height (cm)	172 ± 9	167 ± 8	169 ± 11	171 ± 10	174 ± 9
Preinduction fentanyl dose (μg/kg)	3.1 ± 0.6	0	3.0 ± 0.5	5.9 ± 1.2	8.9 ± 1.1
Thiopental dose (mg/kg)	4.4 ± 1.5	5.7 ± 1.1	4.2 ± 0.9	3.6 ± 1.4[a]	3.4 ± 0.9[a]
Temperature at incision (°C)	36.0 ± 0.6	36.1 ± 0.4	36.1 ± 0.5	36.0 ± 0.3	35.9 ± 0.6
Induction to incision (min)	19 ± 6	23 ± 7	20 ± 6	21 ± 5	20 ± 6

All values except for *n* and sex are expressed as mean ± SD.
Patients in group 1 received isoflurane; those in groups 2–5 received desflurane.
[a] Significantly different from group 2, $P < 0.05$.

In group 1 (isoflurane), MAC was 0.4% ± 0.05%. Desflurane MAC was 3.7% ± 0.5%, 3.0% ± 0.4%, 1.2% ± 0.2%, and 0.1% ± 0.1% in groups 2–5, respectively. In fact, in the high-dose fentanyl group (5), there was no movement recorded in any subject except the one patient who did not receive any desflurane before incision. Therefore, because only one bracketed interval could be obtained in this treatment group, the variability was assumed to be equivalent to the accuracy of the Datex gas analyzer (±0.1%). As expected, fentanyl produced a dose-dependent decrease in the MAC of desflurane (Figure 1). Factors known to alter MAC (e.g., age, temperature) were equivalent in the movers and nonmovers within each treatment group.

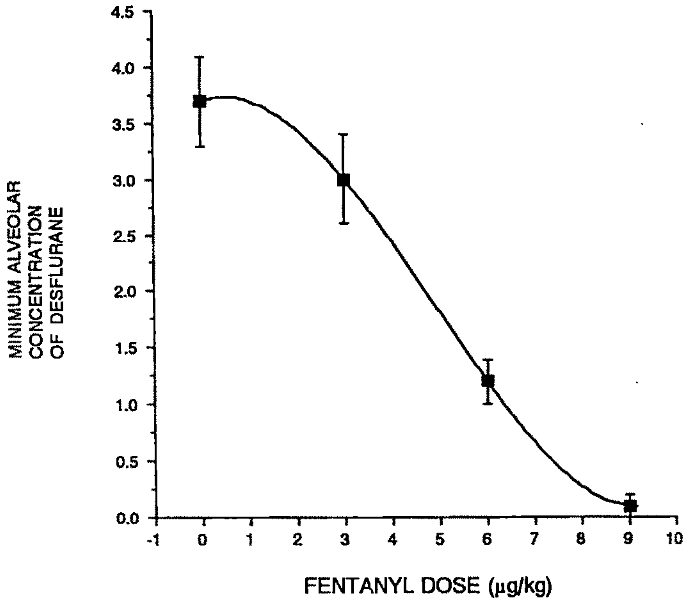


Figure 1. Preinduction doses of fentanyl decreased the end-tidal desflurane concentration required to prevent movement in response to skin incision in a dose-dependent fashion. Minimum alveolar concentration (MAC) values are reported as mean ± SD. A hyperbolic equation was used to fit these data points to illustrate the asymptotically limiting values of MAC at either end of the dose-response curve.

Discussion

The anesthetic potency (MAC) of desflurane, when used alone, has been determined in several species, including rats (5.7%), dogs (7.2%), pigs (10%), and humans (6.0%) (2,6–8). However, information regarding the interaction of this new inhaled anesthetic with commonly used anesthetic, analgesic, and muscle relaxant drugs is needed before its introduction into clinical practice. Both N_2O and opioid analgesics decrease the MAC of commonly used volatile anesthetics (e.g., halothane, isoflurane, and enflurane) (9–12). The effect of N_2O on the desflurane MAC has recently been investigated in humans (13).

Previous studies have indicated that N_2O decreases the MAC of volatile anesthetics in a concentration-dependent, linear fashion (9,10,14,15). Although this assumption has recently been questioned (16), current data suggest that the MAC of desflurane is decreased from 6% to approximately 3% when administered with 60% N_2O in O_2 (2,13). In this study we found the isoflurane MAC in the presence of 60% N_2O and 3 μg/kg fentanyl to be 0.4% ± 0.06%. This value is consistent with the reported MAC of isoflurane in 70% N_2O of 0.5% ± 0.07% in patients aged 46 ± 1 yr in the absence of any opioid analgesic (10). Our data suggest that fentanyl in a dose of 3 μg/kg decreases the MAC of isoflurane-N_2O by an additional 20%. We observed a similar effect on desflurane MAC. Thus, the increase in anesthetic potency produced by 3 μg/kg IV fentanyl appears to be similar with both desflurane and isoflurane. The overall results suggest a dose-related decrease in the desflurane anesthetic requirement for skin incision as the amount of fentanyl is increased (Figure 1), with MAC approaching zero when 60% N_2O is administered with 9 μg/kg fentanyl and 2–4 mg/kg thiopental for induction of anesthesia.

There are two major deficiencies in our study design. First, within each treatment group, the induction dose of thiopental was titrated to a clinical endpoint (i.e., loss of the eyelid reflex). Not surprisingly, patients in the low-dose fentanyl groups (1 and 3) required slightly more thiopental for induction than did those in the high-dose fentanyl groups (4 and 5). This difference in the barbiturate requirement may have altered the response at the time of skin incision. However, it is unlikely that this finding significantly affected our MAC data as the average time from induction to incision was at least 19 min in each group, with an overall mean (± SD) of 20 ± 6 min in all five groups.

Pharmacokinetic studies have reported the rapid distribution (α) half-life of thiopental to be 2.5–8.5 min, and the slow distribution half-life to be 46–63 min, with an elimination half-life of 5.1–11.6 h (17,18). However, using direct measurements of cerebral blood flow with carotid arterial and internal jugular venous blood sampling, it has been shown that the blood (and brain) concentration of thiopental in humans is less than one-tenth the peak concentration 20 min after an intravenous bolus injection (19). In addition, pharmacodynamic studies of thiopental that have examined the loss of the corneal reflex and response to trapezius muscle stimulation indicate that these responses would have returned to baseline within 20 min after an induction dose of thiopental (20). Finally, thiopental has no analgesic properties, and low concentrations would be expected to have little (if any) effect on the MAC of desflurane (21). For these reasons, the differences in the induction doses of thiopental between the desflurane treatment groups would not be expected to affect the outcome of the MAC determinations significantly.

A second shortcoming in our study design relates to the fact that fentanyl was administered as an IV bolus dose over 2–5 min before induction of anesthesia with thiopental. Consequently, true pharmacokinetic steady-state levels of fentanyl were not present at the time of skin incision. Although a continuous fentanyl infusion has been utilized to provide constant plasma fentanyl concentrations during MAC studies in dogs (11,22), our study was designed to reflect the method in which both fentanyl and thiopental would likely be used with desflurane in clinical practice (i.e., as IV bolus doses). Obviously, the curve shown in Figure 1 would be shifted to the right as the time between fentanyl injection and skin incision increased.

In summary, we determined the MAC of desflurane in the presence of 60% N_2O in patients given an IV induction dose of fentanyl ranging from 0 to 9 μg/kg. Fentanyl, 3 μg/kg IV, enhances the anesthetic potency of desflurane to a similar degree to that of isoflurane when these volatile agents are given with N_2O. Furthermore, there is a dose-effect relationship between the amount of fentanyl administered at the time of induction and the decrease in the desflurane anesthetic requirement.

The authors thank the staff, residents, and CRNAs in the Department of Anesthesiology at Washington University for their cooperation during the study, as well as Dr. Matthew Bodner for his assistance in the preparation of the manuscript.

References

1. Eger EI. Partition coefficients of I-653 in human blood, saline, and olive oil. Anesth Analg 1987;66:971–3.
2. Rampil IJ, Zwass M, Lockhart S, et al. MAC of I-653 in surgical patients. Anesthesiology 1989;71:A269.
3. Eger EI, Saidman LJ, Brandstater MB. Minimum alveolar concentration: a standard of anesthetic potency. Anesthesiology 1965;26:756–63.
4. Dixon WJ. Quantal response variable experimentation: the up-and-down method. In: McArthur JW, Colton T, eds. Statistics in endocrinology. Cambridge, Mass.: MIT Press, 1970; 251–67.
5. Saidman LJ, Eger EI II, Munson ES, Babad AA, Muallem M. Minimum alveolar concentration of methoxyflurane, halothane, ether and cyclopropane in man: correlation with theories of anesthesia. Anesthesiology 1967;28:994–1002.
6. Eger EI, Johnson BH. MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. Anesth Analg 1987;66;974–6.
7. Doorley BM, Waters SJ, Terrell RC, Robinson JL. MAC of I-653 in beagle dogs and New Zealand white rabbits. Anesthesiology 1988;69:89–91.
8. Eger EI, Johnson BH, Weiskopf RB, et al. MAC of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. Anesth Analg 1988;67:1174–6.
9. Saidman LJ, Eger EI. Effect of nitrous oxide and of narcotic premedication on the alveolar concentration of halothane required for anesthesia. Anesthesiology 1964;25:302–6.
10. Stevens WC, Dolan WM, Gibbons RT, et al. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. Anesthesiology 1973;42:197–200.
11. Murphy MR, Hug CC. The anesthetic potency of fentanyl in terms of its reduction of enflurane MAC. Anesthesiology 1982;57:485–8.
12. Saidman LJ, Eger EI. Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. Anesthesiology 1964;26:134–9.
13. Rampil IJ, Lockhart SH, Zwass MS, Eger EI. Effects of age or nitrous oxide on the MAC of desflurane (abstract). Anesth Analg 1990;70:S319.

14. Stoelting RK. The effect of nitrous oxide on the minimum alveolar concentration of methoxyflurane needed for anesthesia. Anesthesiology 1971;34:353–5.
15. Torri G, Damia G, Fabiani ML. Effect of nitrous oxide on the anesthetic requirement of enflurane. Br J Anaesth 1974;46:468–72.
16. Cole DJ, Kalichman MW, Shapiro HM. The nonlinear contribution of nitrous oxide at sub-MAC concentrations to enflurane MAC in rats. Anesth Analg 1989;68:556–62.
17. Ghoneim MM, Van Hamme MJ. Pharmacokinetics of thiopentone—effects of enflurane and nitrous oxide anesthesia and surgery. Br J Anaesth 1978;50:1237–41.
18. Hudson RJ, Stanski DR, Burch PC. Pharmacokinetics of methohexital and thiopental in surgical patients. Anesthesiology 1983;59:215–9.
19. Price HL, Kovnat PJ, Safer JN, Conner EH, Price ML. The uptake of thiopental by body tissues and its relation to the duration of narcosis. Clin Pharmacol Ther 1959;1:16–22.
20. Becker KE. Plasma levels necessary for anesthesia. Anesthesiology 1978;49:192–6.
21. Dundee JW. Intravenous anaesthetic agents. Chicago: Year Book Medical Publishers, 1979:7–12.
22. Schwieger IM, Hall RI, Hug CC. Midazolam and fentanyl interaction in reducing enflurane MAC (abstract). Anesthesiology 1988;69:A559.

Historical Article

Gardner Quincy Colton: Pioneer of Nitrous Oxide Anesthesia

Gary B. Smith, BM, FFARCS, and Nicholas P. Hirsch, MB, BS, FFARCS

Key Words: HISTORY, GARDNER QUINCY COLTON. ANESTHETICS, GASES—Gardner Colton.

At the fiftieth anniversary celebration of Horace Wells' discovery of the anesthetic properties of nitrous oxide in Philadelphia, Professor Garetson, presiding officer of the United States Dental Association, commented: "Had there been no Colton, there would have been no Wells" (1). Although this may well be true, Colton, for his part, claimed very little reward for his involvement in one of the most important events in the history of the speciality of anesthesia. His modest and humble personality has ensured that his varied and eventful life story is poorly known to anesthetists.

Gardner Quincy Colton (Figure 1) was born in Georgia, Vermont, a small village on the shores of Lake Champlain, on February 7, 1814. His father, Deacon Walter Colton, a poor but deeply religious weaver, was descended from Quartermaster George Colton who had sailed from England in the early 1600s and had settled in Springfield, Massachusetts. Gardner's mother was Thankful (Cobb) Colton (2). Gardner, the youngest of 12 children,* 10 sons and two daughters, recalls:

> Being the youngest of the family, I was the last to be provided for. . . . I had to wear the mended and patched garments of my older brothers which were reduced to my size. . . . Many a time I would wake up in the morning and find a snow drift on my bed, the snow having blown through the leaky roof. I think I did not have an overcoat till I was near twenty years of age (3).

At the age of 14, Gardner went to work on a farm for one of his brothers. His father had hoped that Gardner would attend college, but he had to give up because of poor eyesight (5). For 5 years he was apprentice to Mr. Azel Church, a chairmaker in St. Albans, Vermont (6). Allowed five dollars a year for spending money but requiring more, Gardner rang the church bell at six o'clock in the morning, receiving one dollar from each local merchant for the service (3). Colton's story continues:

> After finishing my apprenticeship in 1835, I came to New York and commenced work as a journeyman. I was set to making birds' eye-maple and scroll-top cane-seat chairs. After a few months' practice, I got so that I could easily make one dozen a day, for which I was paid $2.50 a dozen, or $15 a week. I paid $2.50 a week board (3).

After working several years at chairmaking, Colton married Eleanor Pomeroy on November 28, 1839. Their only child, Ellen Kathleen, was born on September 21, 1840. Sadly, Eleanor died on February 10, 1841 (2). Colton's older brothers then offered to help him through medical school if he desired. Gardner eagerly accepted (3).

Colton entered the Crosby Street College of Physicians and Surgeons in New York in 1842 (6) at the age of 28. He studied under Robert Watts, Jr., Professor of Anatomy and Physiology, and Willard Parker, Professor of Surgery (7) (Figure 2). However, after 2 years, having taken no degree (5), he decided to "throw physic to the dogs" and went off to lecture on chemistry and natural philosophy. Nitrous oxide was one of the subjects on which he lectured.

Colton had probably learned of the effects of nitrous oxide gas during his medical studies (5), as it is likely that medical students often experimented

---

Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication November 1, 1990.

Address correspondence to Dr. Smith, Department of Anaesthesia, Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY, United Kingdom.

*Colton, in his text *Boyhood Recollections—A Story With a Moral* (4), comments that there were only 11 offspring. He forgets that one brother, Luther, Calvin's twin, lived for only 15 days.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

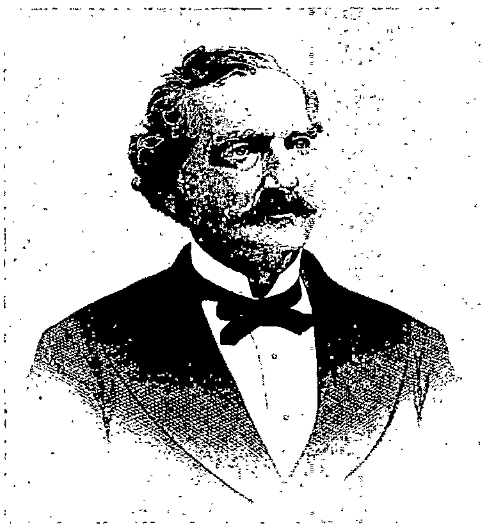


Figure 1. Gardner Quincy Colton (1814–1898) from an engraving by George E. Perrine of New York (Yale Medical Historical Library, New Haven, Conn.).

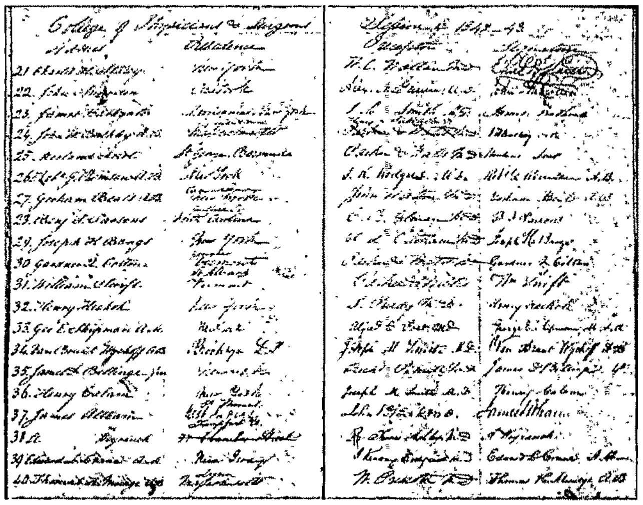


Figure 2. Registration ledger from the Crosby Street College of Physicians and Surgeons (now Columbia University) for 1842 and 1843, demonstrating Colton's signature against his entries on line 30 as student to Robert Watts, Jr., and Willard Parker. (Published with permission of the Augustus C. Long Health Sciences Library, Columbia University, New York, N.Y.)

with the gas. In addition, exhibitions of the effects of "laughing gas" given by itinerant lecturers in the United States have been documented since the 1830s (8), when Samuel Colt, in the guise of Dr. S. Coult, presented a show in an attempt to fund the patent for his revolver. Before Colton finished his medical studies, he gave a series of lectures on chemistry to a young ladies' seminary in New York. A demonstration of nitrous oxide was included in the experiments and under the gas' exhilarating influence the young ladies laughed and danced (3).

His fellow students learned that Colton could make the gas and asked if he could do so for them. He obliged and they "had lots of fun with it in the anatomical lecture room" (3). One student suggested that Colton put on an exhibition of the gas in the Broadway Tabernacle in order to make some money. This Colton did in the spring of 1844:

> I went to Mr. Hale, proprietor of the *Journal of Commerce*, who owned the Tabernacle, laid the matter before him, but said that I had no money. He finally agreed that I might have the Tabernacle one evening for $50, and pay him after the exhibition. I then wanted $75 to get out bills and advertise. . . . The tickets were put at twenty-five cents each, and I gave away a good many in order to be sure of a respectable show. Well, the affair came off, and my receipts were $535! I cleared over $400 above all my expenses (3).

The exhibition was reported by N. P. Willis in "Diary of Town Trifles" in the *New Mirror* of April 6 (9). Between three and four thousand people attended the event. A platform in the hall was hemmed in by benches, and it was advertised that "twelve strong men" would be there to prevent injury to the spectators. After some impatience on the part of the audience, Dr. Colton appeared with his specimen of the "highest possible heaven" in an India rubber bag. However, a "thick necked and bony youth" got possession of the bag and, after inhaling its contents, assaulted Colton. The "twelve strong men" rushed to the rescue, the audience applauded, and the lad returned to his senses. It is reported that "A dozen others took their turn and were variously affected"; one participant even acting out a scene from Richard the Third! (9)

The success of this initial exhibition spurred Colton on to further similar exhibitions throughout New England. Tuesday, December 10, 1844, found his show at Hartford, Connecticut. The now famous bill in the *Hartford Courant* advertised the event:

> *A Grand Exhibition of the effects produced by inhaling nitrous oxide, Exhilarating or Laughing gas will be given at Union Hall this Tuesday evening. Forty gallons of gas will be prepared and administered to all in the audience who desire to inhale it. Twelve young men have volunteered to inhale the gas to commence the entertainment. Eight strong men are engaged to occupy the front seats to protect those under the influence of the gas from injuring themselves or others. This course is adopted that no apprehension of danger may be entertained. Probably no one will attempt to fight. The effect of the gas is to make those who inhale it either laugh, sing, dance, speak or fight according to the leading trait of their character. They seem to retain consciousness enough to not say or do that which they would*

> *have occasion to regret. Note that the gas will be administered only to gentlemen of the highest respectability. The object is to make the entertainment in every respect a genteel affair (10).*

Amongst the audience that evening were two men whose involvement in the events of the evening were to be absolutely vital to the introduction of anesthesia. These were Horace Wells, a local dentist, and Samuel A. Cooley, a druggist's assistant. Colton recalls (3):

> I gave the gas to a young man by the name of Cooley, and while under its exhilarating influence he began to dance and jump about. He ran against some wooden settees on the stage, and bruised his shins badly. As the effect of the gas passed off, he took his seat next to Dr. Wells, who said to him, "You must have hurt yourself." Cooley began to feel some pain then, and was astonished to find his legs all bloody. He said he did not feel a particle of pain till the effects of the gas had passed off. While the audience were going out, Dr. Wells said to me "Why cannot a man have a tooth pulled while under the gas and not feel it?" I replied that I did not know. Dr. Wells said he believed it could be done, and would try it on himself if I would bring a bag of gas to his office. The next day I went to his office with a bag of gas. Dr. Wells called in Dr. Riggs, a neighbouring dentist, to draw his tooth. I gave the gas and Dr. Riggs took out the tooth. On recovering, and finding his tooth out, Dr. Wells exclaimed, *"It is the greatest discovery ever made. I didn't feel it so much as the prick of a pin!"* That was the first tooth ever drawn without pain (3).

The exact details of events surrounding the episode recounted above vary in small amounts depending on the time and storyteller. For instance, Cooley, speaking at the 37th Congress in the United States Senate on February 14, 1863 (11), suggests that he inhaled nitrous oxide at a private sitting given by Colton at the Union Hall on Tuesday, December 11, 1844, the day after Colton's public demonstration of the gas. He says that it was at this meeting, attended by Wells, Colton's brother Calvin, Benjamin Moulton, and others, that he bashed his shin. Cooley also remarks that the "tooth-pulling incident" took place later that same day (11). Colton, however, in a letter to the *New York Times* of 1862 entitled "The Invention of Anaesthesia" (12), singles out Wells as having taken nitrous oxide, run against a bench, and "bruised his leg severely." It is also alleged (6) that Colton told Wells that, at an earlier exhibition of nitrous oxide given by him in Bridgeport, Connecticut, a young man, in striking another, had broken a bone in one of his hands, but had been unaware of it until the effects of the gas had worn off. One further controversy exists and surrounds the question of who actually administered the nitrous oxide gas to Wells on the occasion of the tooth extraction. Colton clearly states in his writings (3,12–19) that it was he, and this is confirmed by Cooley (11). John M. Riggs, the dentist who extracted the diseased molar from Wells, in a letter written in 1872 (20), suggests, however, that:

> Wells took the bag in his lap—held the tube to his mouth and inhaled till insensibility relaxed the muscles of his arms—his hands fell on his breast—his head dropped on the headrest. . . . Mr. Colton, Cooley and the two others stood by the open door ready to run out if Wells jumped up from the chair.

He continues:

> For the credit of Dr. Colton I can say—he made the gas—gave a bag of it to Dr. Wells to experiment with—witnessed the operation of extracting the first tooth and went on his way to other cities.

Earlier, in the same letter, having suggested that Colton's "object was to make money and nothing else," Riggs states that Colton knew nothing of the discussion Wells and Riggs had on the night of December 10, 1844, and their "determination to try the gas on Wells the next morning" (20).

In many letters and pamphlets written later on in life, Colton's story becomes more consistent regarding the date and sequence of events (3,13–16,19). However, despite the earlier inconsistencies, Colton remained true in his support for Wells as the discoverer of anesthesia. In his pamphlet "ANAESTHESIA. Who made and developed this great discovery?" he writes about the extraction of Well's tooth (13): "This was the FIRST operation performed in modern anaesthesia, and was the forerunner of all the other anaesthetics. Beyond all question, this discovery had its birth in the brain of Dr. Horace Wells!"

After the success of the tooth pulling, Colton taught Wells how to manufacture nitrous oxide, and, with the assistance of Dr. Riggs, Wells used it for both dentistry and surgery (11,12,21). In January 1845 Wells went to Boston to demonstrate the use of nitrous oxide to the students of Harvard Medical School. However, the young boy receiving the nitrous oxide for a dental extraction cried out during the procedure (16,19), and Wells was hissed out of the room as a fraud. Wells returned to Hartford and continued to use the gas in his practice (19), but the introduction of ether, and Wells' subsequent trip to Europe, soon ousted memories of nitrous oxide. Meanwhile, Colton continued his lectures on chemistry and natural philosophy and occasionally gave lectures on "laughing gas."

Over the next few years Colton became involved in two major scientific inventions—the telegraph and the electric engine. First, he became friends with Professor Samuel F. B. Morse, inventor of the telegraph and was involved in the first telegraph message ever to be received in New York. In his book *Boyhood and Manhood Recollections. The story of a busy life* (3), Colton writes:

> About this time, Professor Samuel Morse took me into his office and gave me full instructions in regard to the construction and operation of his magnetic telegraph, and afterwards allowed me to announce a lecture on the telegraph under his "auspices," in the Broadway Tabernacle. . . . Professor Morse said I made one or two slight mistakes in my lecture, but on the whole he was so well pleased with it that he gave me . . . a letter of unqualified recommendation to the public as being able to explain his telegraph. With this letter I travelled and lectured all over the United States.

While lecturing on the telegraph, Colton, using the principles of the electromagnet, conceived the idea of an electric engine that could be driven on a track. According to Mr. George Prescott, author of *Dynamo-Electricity* (1885) (22), Colton was the first man to apply electricity to the "propulsion of cars." Gardner took his plans for the engine to a machinist named Lilly, who manufactured it. Attached to the engine were two or three passenger cars filled with dolls for passengers. It was one of the first motors in electric railroad history and figured in a patent suit involving Oliver Kelly, the General Electric Company, and the Springfield Railway Company (23). Importantly, it differed from other such engines because electricity was applied to the track rather than to the engine itself. The engine (Figure 3), measuring 5" × 12" × 8", consisted of two magnets so arranged that metal bars placed on the ends of the rocking arm were attracted as the magnets were alternately energized. A reciprocal motion was imparted to the arm and then transmitted through a driving rod to a wheel geared to the driving wheels of the chassis. It ran on a circular railroad about 6–8 ft in diameter around Colton's office in the Cooper Union, New York, and is now displayed, minus the passenger cars, in the Smithsonian Institute in Washington.

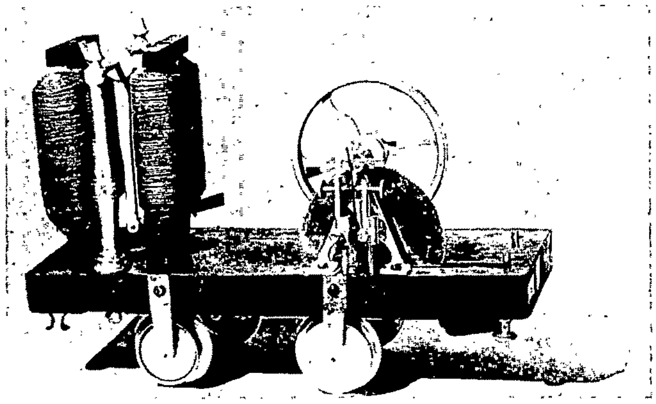
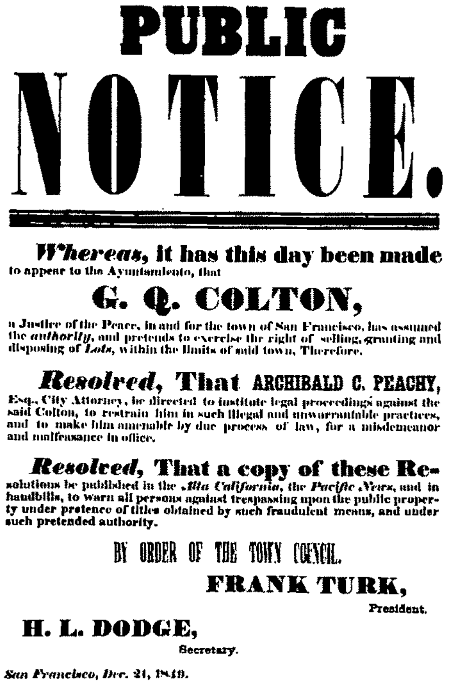


Figure 3. Electric engine, invented by Colton, currently on display at the Smithsonian Institute, Washington, D.C. (Courtesy of the National Museum of American History, Smithsonian Institute, Washington, D.C.) The engine measures 5" × 12" × 8".

In 1849, after his brother Walter's appointment as Civil Governor of California, Gardner sailed on the steamer Panama around Cape Horn to join him in San Francisco (24). Walter, who had been Naval Chaplain on the USS Congress during the War with Mexico, had already established California's first newspaper *The Californian*, set up trial by jury, reported the discovery of gold in California to the East Coast states, and built California's first schoolhouse (5,25). Gardner arrived in San Francisco on May 10, 1849, and soon became caught up in the Gold Rush of that year. To provide an income for himself he practiced medicine, prospected for gold, and ferried miners across deep fast-flowing mountain streams using an India rubber boat (24). As there were no coins in circulation, Colton took a "pinch" of gold dust in exchange for the 50-cent fee for the river crossing. However, he soon learned that "a fellow with a broad thumb and big finger would 'pinch' $2." During the rainy season it was impossible to work the mines, and he returned to San Francisco. In partnership with another, he opened a hospital using money borrowed at 10% per month interest. So successful was this venture that only months after the hospital had opened he was able to send a bank draft of $10,000 back to his second wife Emily in New York (3).

In the late fall of 1849, despite having no legal background, Colton was appointed as the first Justice of the Peace for San Francisco by Governor Riley and Prefect Horace Hawes. As a result, he found himself in charge of the coroner's business, all trials for causes under $100, and the controversial matter of the sale of town lots in the city. After the formation of the State of California in November 1849, a great deal of confusion existed regarding the ownership of land in San Francisco. However, acting under the powers that he believed had been granted to him, Colton commenced selling city lots, often at bargain prices (26). Believing Colton to be acting without authority, the Town Council took action on December 21.



PUBLIC

NOTICE.

Whereas, it has this day been made to appear to the Ayuntamiento, that

G. Q. COLTON,

a Justice of the Peace, in and for the town of San Francisco, has assumed the *authority*, and pretends to exercise the right of selling, granting and disposing of *Lots*, within the limits of said town, Therefore,

***Resolved*, That ARCHIBALD C. PEACHY,** Esq., City Attorney, be directed to institute legal proceedings against the said Colton, to restrain him in such illegal and unwarrantable practices, and to make him amenable by due process of law, for a misdemeanor and malfeasance in office.

***Resolved*, That a copy of these Re**solutions be published in the *Alta California*, the *Pacific News*, and in handbills, to warn all persons against trespassing upon the public property under pretence of titles obtained by such fraudulent means, and under such pretended authority.

BY ORDER OF THE TOWN COUNCIL.

FRANK TURK,
President.

H. L. DODGE,
Secretary.

San Francisco, Dec. 21, 1849.

ALTA CALIFORNIA PRESS

Figure 4. Public Notice from San Francisco, dated December 21, 1849, "outlawing" the sale of land in the city by Colton. (Beineke Rare Book & Manuscript Library, Yale University, New Haven, Conn.)

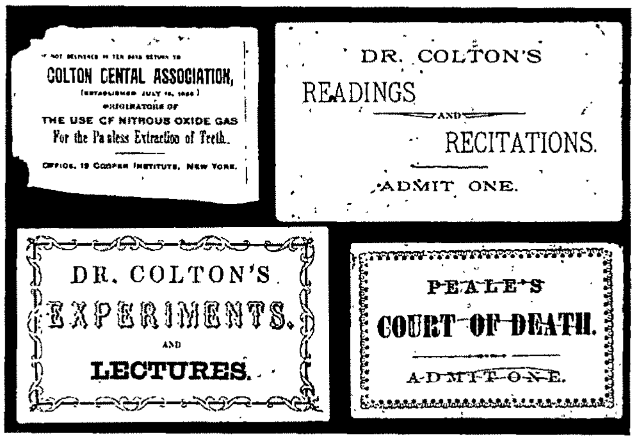

IF NOT DELIVERED IN TEN DAYS RETURN TO
COLTON DENTAL ASSOCIATION,
(ESTABLISHED JULY 16, 1863)
ORIGINATORS OF
THE USE OF NITROUS OXIDE GAS
For the Painless Extraction of Teeth.
OFFICE, 19 COOPER INSTITUTE, NEW YORK.
DR. COLTON'S
READINGS
AND
RECITATIONS.
ADMIT ONE.
DR. COLTON'S
EXPERIMENTS.
AND
LECTURES.
PEALE'S
COURT OF DEATH.
ADMIT ONE.

Figure 5. Artifacts belonging to Colton. *Upper right* is an entry ticket for Dr. Colton's Readings and Recitations; *lower right* is an admission ticket to Colton's exhibition of Rembrandt Peale's celebrated picture "The Court of Death," displayed by Colton at his shows in the 1840s; *upper left* is an address label for the Colton Dental Association; *lower left* is an admission ticket for Colton's Experiments and Lectures. (Courtesy of Mrs. R. Butler.)

Archibald Peachey, a city attorney, was directed to institute legal proceedings against Colton and to restrain him from such "illegal and unwarrantable practices" (27) (Figure 4).

The city council adopted the following resolution on December 24, 1849: *"Resolved, that the Town Council hereby declares all grants of town lots made and signed by G. Q. Colton, Justice of the Peace, void and of no effect, the same having been . . . illegally made"* (27). Colton replied:

> I received my commission as Justice of Peace from Mr. Hawes, Prefect of this district, about the first of November last. It was sent to Monterey and came back 'approved by the Governor' about the 15th of the same month, as near as I can recollect. . . . I made the grants, first because I believed, and still believe the law authorized me to make them. Second, because I believed, and still believe it the most equitable mode of distributing the public lands. Third, because I was instructed to make them by the Prefect (27).

Rather remarkably, Prefect Hawes then stated: "I never ordered Mr. Colton to make any grants of land, nor did I ever see his face to my recollection" (27).

Colton contended that the cases brought against him were abandoned before trial (3), but confusion continued to reign in San Francisco for some time afterward over the ownership of land titles known thereafter as the "Colton Grants" (28). Colton left California a rich man (5,29), and the record is blurred as to whether he ever made any accounts of the proceeds of lands sold by him.

After arriving home, Colton "floated about several years doing little or nothing." He spent one winter in Boston, writing paragraphs and reporting sermons for the *Boston Transcript*. Many authors have suggested that in his wanderings from town to town, Colton began to compile and publish a series of war maps that bear his name (1,5,29,30). However, in his copious writings, Colton never mentions this, and it is more likely that they were produced by a very distant relative, Joseph Hutchings Colton, who was world-renowned for the manufacture of maps, atlases, and school biographies (2).

About this time, Gardner invested much of his money in the ill-fated Salt Works of Syracuse. Having rapidly lost his investment, he resumed his lectures and laughing gas exhibitions (Figure 5). After Wells' death, the use of nitrous oxide for all anesthetic purposes had ceased; Colton was solely responsible for its reintroduction. Again, the exact details relating to events at this time are a little blurred. In one of his writings Colton comments that he was persuaded to administer nitrous oxide for dental surgery to a lady in New Britain, Connecticut, in the summer of 1862 (16). It is reputed that when Colton returned to New Britain in 1863, he found that the local dentist, later identified as Dr. R. C. Dunham (31), had subsequently administered the gas to more than 600 patients (16). Colton states that he and Dunham then joined forces with another dentist, one Joseph H. Smith of New Haven, Connecticut, for 3 weeks in the summer of 1863 (16,32). In Colton's other writings his story is somewhat different (3,13,14,17,19). These other versions allege, for example, that in June 1863 Colton visited New Haven, Connecticut, for another of his exhibitions. He invited a number of gentlemen to attend a private preliminary entertainment at which he gave a history of the discovery of anesthesia, stating also that he had never been able to encourage a dentist to try the gas. A local dentist, Joseph H. Smith of Olive Street, New Haven, who was present, agreed to try the gas provided Colton administered it. The next day they extracted seven teeth from a well-known wealthy lady using nitrous oxide as the anesthetic. After the successful extractions the woman said, "Don't go, doctor; I want to give you my blessing!" She indicated that Colton could mention her name to his audience and state the fact that she had had seven teeth drawn, while under the gas, without any pain or unpleasant effects.

Colton then abandoned the "Exhibition" business and agreed on a partnership with Smith. Colton would provide and administer nitrous oxide for 1 week and Smith would extract the teeth. They were so successful that they continued for 23 days, during which time they extracted "a little over 3,000 teeth!" (17). Colton, ever an entrepreneur, writes:

> Thinks I, this is a better business than lecturing, sometimes to a "beggarly account of empty boxes." . . . I at once determined to go to New York and establish an institution devoted exclusively to the extraction of teeth with the gas. The gas had laid dead and forgotten as an anaesthetic for seventeen years . . . when I revived it. . . . The world is indebted to me for the gas. . . . I opened my office in the Cooper Institute in July 1863, and called my institution "The Colton Dental Association" as my name had been so long identified with the gas (3).

By November 1863 Colton had associated himself with two eminent New York City dentists, Dr. John Allen and his son William, and they began to devote their time exclusively to the use of nitrous oxide for the extraction of teeth at the Colton Dental Association. The dental and medical professions declared, however, that the gas had been used years before without much success, and thus, initially, Colton and his colleagues were the target of ridicule, sarcasm, and misrepresentation. Month after month, their expenses exceeded their receipts and during the first year it is alleged that Colton spent $8000 in advertising, advocating, and defending, "his invention" (6).

Gradually, business and support increased and over the next few years nearly all the leading dentists of New York sent patients requiring an anesthetic to Colton. According to *The New York Times,* his office was known to "seven out of every ten New Yorkers who had ever lost their sleep from troublesome grinders" (1). From the commencement of records on February 4, 1864, until 1897, more than 193,800 patients were recorded as having had nitrous oxide at the Colton Dental Association (Figure 6). The patients' ages ranged from 3 to 90 years, and there were apparently no fatalities (3). Colton claimed to use about 300 gallons a day at this time (14). In 1865 Colton used nitrous oxide during three surgical operations—a mastectomy and two limb amputations—performed by J. M. Carnochan (33).

Despite Colton's background in medicine and chemistry, and his unrivaled expertise in the administration of nitrous oxide, he remained unaware of the true chemical and physiological effects of the gas. This can be seen from his writings:

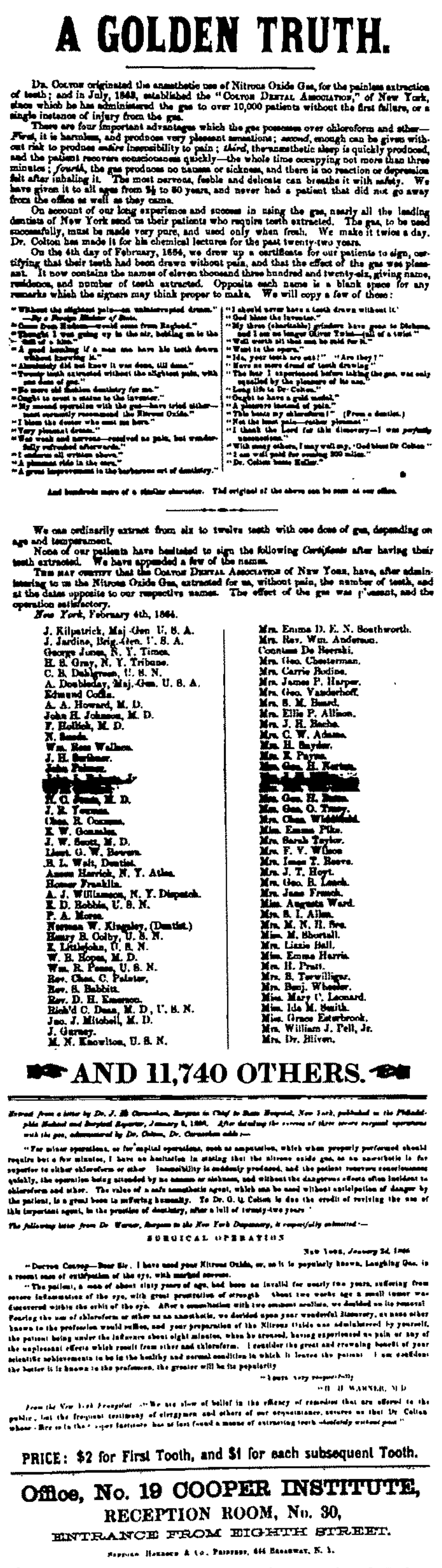
> It is composed of precisely the same elements—oxygen and nitrogen—as the common air, only the proportions are different. . . . In this gas there is half oxygen and half nitrogen, or by volume, one of oxygen to two of nitrogen. Oxygen is the life-giving principle of the air, and in the gas *we have more of it;* a person *lives a little faster* while under its influence. . . . The laughing gas . . . [in contrast to chloroform and ether] . . . acts as an *exhilarant,* as by supplying an extra supply of oxygen to the lungs, the pulse is increased 15 to 20 beats to the minute (13).

Many critics contended that nitrous oxide produced insensibility from asphyxia, not anesthesia (34,35). In response to such criticism, Colton wrote:

> Dr. Foster says: 'That it [nitrous oxide] cannot support respiration or life but a few moments, is seen in that frightful gasping of the patient, growing deeper and faster, *as he dies for want of air.' These symptoms never attend the operation where the quantity breathed from* is large enough (36).

and:

> Dr. Richardson has probably only seen the gas given for exhilaration, where a two or three gallon bag was used. Now if anaesthesia is attempted by the use of such a bag, *the very result which Dr. Richardson describes will follow.* The oxygen—all that sustains life—will be absorbed before anaesthesia is produced. Nothing but nitrogen and carbonic acid remains in the bag, and these, if breathed, will produce asphyxia and insensibility. But let a bag of *eight gallons* of gas be used, and anaesthesia is reached *before* the oxygen is absorbed, and no such ill effects attend the operation (14).



A GOLDEN TRUTH.

Dr. Colton originated the anæsthetic use of Nitrous Oxide Gas, for the painless extraction of teeth; and in July, 1863, established the "Colton Dental Association," of New York, since which he has administered the gas to over 10,000 patients without the first failure, or a single instance of injury from the gas.

There are four important advantages which the gas possesses over chloroform and ether—*First*, it is harmless, and produces very pleasant sensations; *second*, enough can be given without risk to produce *entire* insensibility to pain; *third*, the anæsthetic sleep is quickly produced, and the patient recovers consciousness quickly—the whole time occupying not more than three minutes; *fourth*, the gas produces no nausea or sickness, and there is no reaction or depression felt after inhaling it. The most nervous, feeble and delicate can breathe it with *safety*. We have given it to all ages from 3½ to 80 years, and never had a patient that did not go away from the office as well as they came.

On account of our long experience and success in using the gas, nearly all the leading dentists of New York send us their patients who require teeth extracted. The gas, to be used successfully, must be made very pure, and used only when fresh. We make it twice a day. Dr. Colton has made it for his chemical lectures for the past twenty-two years.

On the 4th day of February, 1864, we drew up a certificate for our patients to sign, certifying that their teeth had been drawn without pain, and that the effect of the gas was pleasant. It now contains the names of eleven thousand three hundred and twenty-six, giving name, residence, and number of teeth extracted. Opposite each name is a blank space for any remarks which the signers may think proper to make. We will copy a few of these:

"Without the slightest pain—an uninterrupted dream."
—*By a Foreign Minister of State.*
"Came from Hudson—would come from England."
"Thought I was going up in the air, holding on to the tail of a kite."
"A good [illegible] if a man can have his teeth drawn without knowing it."
"Absolutely did not know it was done, till done."
"Twenty teeth extracted without the slightest pain, with one dose of gas."
"No more old fashion dentistry for me."
"Ought to erect a statue to the inventor."
"My second operation with the gas—have tried ether—most earnestly recommend the Nitrous Oxide."
"I bless the doctor who sent me here."
"Very pleasant dream."
"Was weak and nervous—received no pain, but wonderfully refreshed afterwards."
"I endorse all written above."
"A pleasant ride in the cars."
"A great improvement in the barbarous art of dentistry."
"I should never have a tooth drawn without it."
"God bless the inventor."
"My three (charitable) grinders have gone to [illegible], and I am no longer Oliver Twist—[illegible]"
"Well worth all that can be said for it."
"Went to the opera."
"Ida, your teeth are out!" "Are they?"
"Have no more dread of tooth drawing."
"The fear I experienced before taking the gas, was only equalled by the pleasure of its use."
"Long life to Dr. Colton."
"Ought to have a gold medal."
"A pleasure instead of pain."
"This beats my chloroform!" (From a dentist.)
"Not the least pain—rather pleasant."
"I thank the Lord for this discovery—I was perfectly unconscious."
"With many others, I may well say, 'God bless Dr. Colton.'"
"I am well paid for coming 300 miles."
"Dr. Colton beats Keller."

And hundreds more of a similar character. The original of the above can be seen at our office.

We can ordinarily extract from six to twelve teeth with one dose of gas, depending on age and temperament.

None of our patients have hesitated to sign the following *Certificate* after having their teeth extracted. We have appended a few of the names.

This may certify that the Colton Dental Association of New York, have, after administering to us the Nitrous Oxide Gas, extracted for us, without pain, the number of teeth, and at the dates opposite to our respective names. The effect of the gas was pleasant, and the operation satisfactory.

New York, February 4th, 1864.

J. Kilpatrick, Maj.-Gen. U. S. A.
J. Jardine, Brig.-Gen. U. S. A.
George Jones, N. Y. Times.
H. S. Gray, N. Y. Tribune.
C. B. Dahlgreen, U. S. N.
A. Doubleday, Maj.-Gen. U. S. A.
Edmund Coffin.
A. A. Howard, M. D.
John H. Johnson, M. D.
F. Hollick, M. D.
N. Sands.
Wm. Ross Wallace.
J. H. Scribner.
John Palmer.
[illegible]
[illegible]
H. C. [illegible], M. D.
J. R. Yeoman.
Chas. B. [illegible]
E. W. Gonzales.
J. W. Scott, M. D.
Lieut. G. W. Bowers.
B. L. Walt, Dentist.
Ammon Herrick, N. Y. Atlas.
Homer Franklin.
A. J. Williamson, N. Y. Dispatch.
E. D. Robbins, U. S. N.
P. A. Morse.
Norman W. Kingsley, (Dentist.)
Henry B. Colby, U. S. N.
E. Littlejohn, U. S. N.
W. B. Hopes, M. D.
Wm. R. Pease, U. S. N.
Rev. Chas. C. Painter,
Rev. S. Babbitt.
Rev. D. H. Emerson.
Rich'd C. Dean, M. D., U. S. N.
Jno. J. Mitchell, M. D.
J. Gurney.
M. N. Knowlton, U. S. N.
Mrs. Emma D. E. N. Southworth.
Mrs. Rev. Wm. Anderson.
Countess De Berski.
Mrs. Geo. Chesterman.
Mrs. Carrie Bodine.
Mrs. James P. Harper.
Mrs. Geo. Vanderhoff.
Mrs. S. M. Beard.
Mrs. Ellis P. Allison.
Mrs. J. H. Bache.
Mrs. C. W. Adams.
Mrs. H. Snyder.
Mrs. E. Payne.
Mrs. Geo. H. Norton.
[illegible]
[illegible]
Mrs. Geo. H. [illegible]
Mrs. Geo. O. Terry.
Mrs. Chas. [illegible]
Miss Emma Pike.
Mrs. Sarah Taylor.
Mrs. F. V. Wilson
Mrs. Isaac T. Reeve.
Mrs. J. T. Hoyt.
Mrs. Geo. B. Leach.
Mrs. Jane French.
Miss Augusta Ward.
Mrs. S. I. Allen.
Mrs. M. N. H. Rea.
Miss M. Shortall.
Mrs. Lizzie Hall.
Miss Emma Harris.
Mrs. H. Pratt.
Mrs. S. Terwilliger.
Mrs. Benj. Wheeler.
Miss Mary C. Leonard.
Miss Ida M. Smith.
Miss Grace Esterbrook.
Mrs. William J. Pell, Jr.
Mrs. Dr. Bliven.

AND 11,740 OTHERS.

PRICE: $2 for First Tooth, and $1 for each subsequent Tooth.

Office, No. 19 COOPER INSTITUTE,
RECEPTION ROOM, No. 30,
ENTRANCE FROM EIGHTH STREET.

Figure 6. Advertisement announcing the work of Colton's Dental Association in the Cooper Institute, New York, N.Y. (Courtesy of the New York Academy of Medicine Library, New York, N.Y.)

Indeed, so convinced was Colton of the beneficial effects of nitrous oxide that he repeatedly inhaled the gas himself (36,37) and also advocated its use as resuscitative therapy in asphyxia! (38). In an interesting insight into Colton's own method of administering the gas and, presumably, into the reason for its safety in his hands despite his ignorance of its chemical composition, Colton remarks on the removal of a "piece of bone from the leg six inches in length" from a boy of 11 years kept in a profound sleep for 3 minutes by alternating the inhalation of nitrous oxide with air (38).

Writing in March 1864, in an attempt to defend the safety of nitrous oxide, Colton critically evaluated three deaths that had been attributed to the use of the gas (38). None were connected with Colton's own practice. He ascertained that one, Mr. Sears of New York, had died of pulmonary congestion; Miss Bell of Swanton, Vermont, had contracted meningitis; and a lady in Allentown, Pennsylvania, had been anesthetized with chloroform and not nitrous oxide! By 1896, he was still able to state: "I doubt if there has ever been a well authenticated case of death caused by the gas, or a death in which there was not some other cause sufficient to produce the result" (37).

For 20 years Colton manufactured his own nitrous oxide using a primitive apparatus that he had designed soon after commencing using the gas as an anesthetic:

> Mr. A. W. Sprague of Boston, Mass., invented an apparatus which I now use in my office and find it altogether the best I have ever seen. . . . First. The *beginner* can hardly fail to make pure gas with it, provided he has pure nitrate of ammonia. Second. After being started, and the ammonia melted, it requires no watching, or even attendance. . . . Third. The passage of the gas through the four washing glass jars controls a "regulator," through which the common coal-gas passes to the burner under the retort, so that *one uniform degree of heat is applied to the retort*, thus preventing the possibility of too great heat. Fourth. The glass tubes in each jar are so made as to break up the nitrous oxides into very minute bubbles in its passage, and thus thoroughly wash it before it reaches the gasometer. . . . Thirty gallons of gas can be made in an hour with it (14).

In the spring of 1867, Colton visited Paris to attend the Universal Exhibition and First International Congress of Medicine. A fellow American, Thomas Wiltberger Evans, was United States Commissioner to the Exhibition. In his report on the dental exhibits, Evans wrote:

> I have observed in the United States Collection in the Exposition . . . an apparatus for the production and

administration of nitrous oxyde gas, exhibited by Dr. J. Q. Colton of New York. It is but just to observe that through the efforts and researches of Dr. Colton, the attention of surgeons has already been directed to the protoxyde of azote or nitrous oxyde gas. . . . Dr. Colton has reestablished by thousands of experiments the superiority of the protoxyde of nitrogen gas over other anaesthetics in Dental Surgery. . . . The gas has recently been employed with success in Paris under my own direction, in the gravest surgical operations (39).

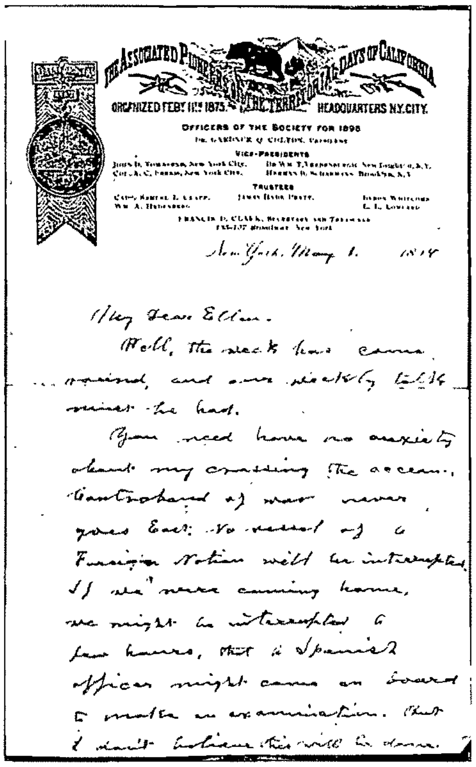
On March 30, 1867, Evans visited London and, using Sprague's apparatus, gave demonstrations of nitrous oxide at the Dental Hospital and at Moorfield's Eye Hospital. The demonstrations were observed with interest but had a mixed reception in the *Lancet* and the *British Medical Journal* (40,41). Convinced of the utility of nitrous oxide, Evans offered the Dental Hospital £100 to be used for the purchase of apparatus and materials to manufacture the gas. The Odontological Society of Great Britain responded by forming a committee to investigate the anesthetic properties of nitrous oxide (42).

Colton, having returned to Paris from his trip around Europe, then traveled to London and on Friday June 5, addressed a meeting of medical and dental practitioners at the house of Mr. C. J. Fox, a dental practitioner (43). He then administered the gas to four patients with complete success and repeated his address 5 days later. Later, Fox went on to champion the cause of nitrous oxide in England. Colton returned home in 1868 and opened dental offices in St. Louis, Chicago, Brooklyn, Cincinnati, Boston, Baltimore, and Philadelphia, all of which operated simultaneously. Apparently, Colton did no extractions himself but hired competent dentists as associates (44).

From his first meeting with Wells, Colton continued to support Wells' claim to be the discoverer of anesthesia. In Colton's own words:

> If I am remembered at all by posterity, it will be on account of my connection with the discovery of anaesthesia. I do not claim that the discovery originated in my mind, only that I was the *occasion* of the discovery, and that I gave the nitrous oxide gas for the *first* surgical operation where pain was destroyed (45).

Colton's determination that Wells should receive recognition for his discovery was reiterated at the 50th anniversary celebrations held on December 10, 1894, at a banquet at Habenstein's Cafe in Hartford under the auspices of the Connecticut State Dental Association (32). At the meeting, during which a tablet was unveiled in memory of Horace Wells, Colton retold the story of the discovery. At the beginning of the meeting, an apology for absence was received from Samuel Cooley, the druggist's assistant who had banged his shin 50 years before and started the whole story of nitrous oxide.



THE ASSOCIATED PIONEERS OF THE TERRITORIAL DAYS OF CALIFORNIA
ORGANIZED FEBY 11th 1875. HEADQUARTERS N.Y. CITY.
OFFICERS OF THE SOCIETY FOR 1896
DR. GARDNER Q. COLTON, PRESIDENT
VICE-PRESIDENTS
TRUSTEES

New York, May 1. 1898

My dear Ellen.

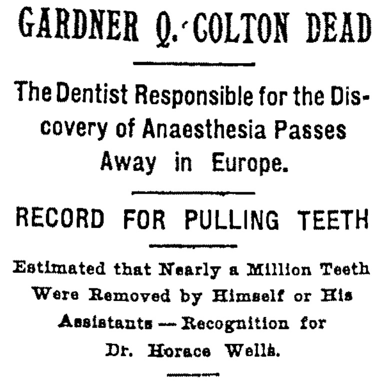
Well, the week has come around, and [illegible] quickly [illegible] [illegible] the last.

You need have no anxiety about my crossing the ocean. Contraband of war never goes East. No vessel of a Foreign Nation will be intercepted. If we were coming home, we might be intercepted a few hours, that a Spanish officer might come on board to make an examination. But I don't believe this will be done.

Figure 7. Letterhead of the "Associated Pioneers of the Territorial Days of California" indicating Colton as president of the Society in 1896. This letter was almost certainly the last written by Colton to his daughter Ellen. (Courtesy of Mrs. R. Butler.)

Colton continued to practice dental anesthesia until, 4 years later, in 1898, he died while visiting Europe. In keeping with the confusion regarding the dates and events surrounding the introduction of nitrous oxide anesthesia, uncertainties have occurred in relation to Colton's death and his subsequent resting place. His obituaries (Figure 8) state that he died in Rotterdam (1,5,29,46) on August 9 (5,46) or August 12, 1898 (29). However, the Colton family records show that he died on August 10, 1898, in Geneva, Switzerland (personal communication, Mrs. R. Butler, Colton's great-granddaughter). Colton's body was returned to the United States where it was cremated and his ashes buried in the Aurora Hill plot of Woodlawn Cemetery in The Bronx, New York City (47) (Figure 9). To add further confusion, the interment register at Woodlawn indicates that Colton died in Germany (47).

Gardner Quincy Colton's life was varied in its extreme. To the activities already described one can add his interests in geology, circuses (he was a good friend of P. T. Barnum), and death. He was a devout



GARDNER Q. COLTON DEAD

The Dentist Responsible for the Discovery of Anaesthesia Passes Away in Europe.

RECORD FOR PULLING TEETH

Estimated that Nearly a Million Teeth Were Removed by Himself or His Assistants — Recognition for Dr. Horace Wells.

Figure 8. Announcement of Colton's death in *The New York Times* of Friday, August 12, 1898. (Copyright © 1898 by *The New York Times* Company. Reprinted by permission.)

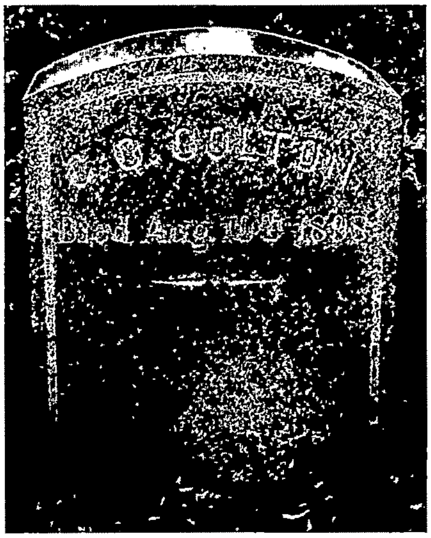


Figure 9. Colton's gravestone in the Aurora Hill plot of Woodlawn Cemetery, The Bronx, New York, N.Y.

Christian and a prolific author of many pamphlets, books, and letters on varied topics. However, without doubt, his great legacy to humanity has been the gift of nitrous oxide anesthesia. Without Colton, it is unclear if this agent would ever have found the position in modern anesthesia that it now holds.

The authors wish to thank the following for their considerable patience and assistance during the preparation of this article: Ruth Butler; Peter Mallett of the Georgia Historical Society; Barbara Lekish of the California Historical Society; Amanda Hegarty of the New York Academy of Medicine; Ferenc Gyorgyey, Susan Alon, and Janice Braun of the Medical History Library of Yale University; Gary Strong of the California State Library; Jan Reeves of the Postgraduate Medical Library of Queen Alexandra Hospital, Portsmouth, United Kingdom; Robert MacLean and Roger Courtney of the Medical Photography Department of Queen Alexandra Hospital, Portsmouth, United Kingdom; and the staff of Woodlawn Cemetery, New York City.

References

1. Anonymous. Gardner Q. Colton dead. *The New York Times*, August 12, 1898, p. 7.
2. Colton GW. A genealogical record of the descendants of Quartermaster George Colton. Lancaster, Pa.: Wickersham Printing, 1912.
3. Colton GQ. Boyhood and manhood recollections. The story of a busy life. New York: A. G. Sherwood, 1897.
4. Colton GQ. Boyhood recollections. A story with a moral. New York: E. M. Day, 1891.
5. Johnson A, Malone D, eds. Dictionary of American Biography. New York: Charles Scribner, 1930.
6. Biographical sketch held by New York Academy of Medicine. Thought to be submitted by G. Q. Colton for publication in a book entitled *Men of Mark*.
7. Records of Health Sciences Library, Columbia University, New York City, N.Y.
8. Haven CT, Belden FA. A history of the Colt revolver. New York: William Morrow, 1940.
9. Willis NP. Diary of town trifles. *The New Mirror*, April 6, 1844, p. 8–9.
10. *Hartford Courant*, December 10, 1844.
11. Reports of the 37th Congress of the United States, 1862–63: 3rd session. Senate Reports Vol. 1, pp. 100–3, February 1863.
12. Colton GQ. The invention of anaesthesia. *The New York Times*, February 5, 1862, p. 8.
13. Colton GQ. Anaesthesia. Who made and developed this great discovery? A statement "delivered upon the mellowing of occasion." New York: A. G. Sherwood, 1896.
14. Colton GQ. Experience in the use of nitrous oxide. Br J Dent Sci 1863;11:253–7.
15. Colton GQ. Who was the discoverer? *The New York Times*, October 21, 1896, p. 4.
16. Colton GQ. Nitrous-oxide. Mon Rev Dent Sur 1873–4;2:26–30.
17. Colton GQ. Origin of anaesthesia. Dent Cosmos 1896;18:7–9.
18. Colton GQ. A wrong righted. Dent Dig 1896;2:666–7.
19. Colton GQ. A true history of the discovery of anaesthesia. A reply to Mrs. Elizabeth Whitman Morton. New York: A. G. Sherwood, 1896.
20. Letter dated September 17, 1872, from Dr. J. M. Riggs to Drs. Hasbrouch and Howland in New York. Held by the Historical Museum of Medicine and Dentistry, Hartford, Conn.
21. Carnochan JM. Nitrous oxide in capital operations. NY Med Surg Rep 1866;14:117–8.
22. Prescott GB. Dynamo-electricity. New York: D. Appleton & Co. 1884.
23. Anonymous. Dr. Colton's invention. *The New York Times*, October 23, 1896, p. 16.
24. Anonymous. Dr. G. Q. Colton. *Oakland Tribune*, Knave section, September 17, 1961, p. 12.
25. California Pioneer Register and Index, 1542–1848. Including inhabitants of California, 1769–1800, and list of pioneers. Extracted from: Bancroft HH. The history of California. Baltimore: Regional Publishing, 1964.
26. Letters of Jonas Winchester, circa 1850. Held by the California Historical Society, San Francisco, Calif.
27. Johnson KM. The Judges Colton. South Calif Q 1975;57:349–60.
28. Soule F, Gihon JH, Nisbet J. The annals of San Francisco. Palo Alto: Lewis Osborne, 1966.
29. The national cyclopaedia of American biography. New York: J. T. White, 1899.
30. Wilson JG, Fiske J, eds. Appleton's cyclopaedia of American biography. New York: D. Appleton, 1887.

31. McManus J. Limited edition pamphlet containing Notes on the history of anaesthesia, The Wells Memorial Celebration at Hartford, 1894, and an early record of dentists in Connecticut. Copy 168 held by Yale University, New Haven, Conn.
32. Latimer JS. Gleanings from proceedings of the Society of Dental Surgeons of the City of New York. Dent Cosmos 1863;5:303–7.
33. Carnochan JM. On anaesthetics. NY Med Surg Rep 1866;14:5.
34. Foster CW. Nitrous oxide not an anaesthetic. Dent Cosmos 1863;5:614–6.
35. Westcott A. Laughing gas. *Syracuse Daily Standard*, January 28, 1864.
36. Colton GQ. Nitrous oxide an anaesthetic. Dent Cosmos 1864–5;6:8–10.
37. Colton GQ. Nitrous oxide gas. Dent Cosmos 1896;18:14–5.
38. Colton GQ. Nitrous oxide an anaesthetic. Dent Cosmos 1863–4;5:490–3.
39. Evans TW. Report upon dental surgery and the material which it employs. Paris Universal Exhibition, 1867, class 11, group 2.
40. Anonymous. A new anaesthetic (editorial). Br Med J 1868;1:332.
41. Anonymous. Medical annotation. A new anaesthetic. Lancet 1868;1:507.
42. Report of Odontological Society of Great Britain, April 6, 1868. Br J Dent Sci 1868;2:196–215.
43. Anonymous. Dr. Colton on protoxide of nitrogen. Br Med J 1868;1:594.
44. Waters RM. Nitrous oxide centennial. Anesthesiology 1944;5:551–65.
45. Letter dated November 20, 1882, from G. Q. Colton to B. J. Lossing of New York. Held by Yale University, New Haven, Conn.
46. McNeille CS. Obituary. Dr. Gardner Quincy Colton. Dent Cosmos 1898;40:874.
47. Interment Records of Woodlawn Cemetery, Bronx, New York, N.Y.

Clinical Reports

Blind Nasal Intubation With Audio-Capnometry

Sota Omoigui, MD, Peter Glass, MD, Dave L.J. Martel, MS, Kenneth Watkins, RRT,
Kent L. Williams, RRT, Sherry M. Whitefield, RRT, and Larry L. Wooten, RRT

Key Words: INTUBATION, TRACHEAL—blind nasal. EQUIPMENT, AUDIO-CAPNOMETER.

Nasotracheal intubation is performed electively for intraoral operations when anatomic abnormalities or disease of the upper airway make direct laryngoscopy difficult or impossible and, occasionally, when long-term mechanical intubation of the lungs is anticipated. Fiberoptic or blind nasotracheal intubation is usually reserved for situations in which direct laryngoscopy would be impossible or induction of anesthesia before neuromuscular blockade would be hazardous. The flexible fiberoptic bronchoscope may not be available, and success may be limited under emergency conditions owing to blood and secretions blurring the field. In these clinical situations, awake blind nasotracheal intubation may be the technique of choice.

To ensure maximum patient comfort and nasal patency and to minimize the chances of epistaxis associated with nasotracheal intubation, the nasal mucosa is anesthetized and constricted with topical cocaine. If cocaine is not available, vasoconstriction may be produced by topical phenylephrine (Neosynephrine). The endotracheal tube is passed through the nares into the oropharynx and advanced toward the glottic opening as long as breath sounds are maximal as detected by listening to exhaled air passing from the proximal end of the tube. This requires the intubator to keep an ear close to the tube connector to detect changes in breath sounds readily. Alternate techniques utilized in enhancing success with blind nasal intubation include observation of condensation in the endotracheal tube (1), inflation of the cuff (2), use of a suction catheter (3), attaching a microphone to the end of the endotracheal tube to magnify breath sound (4), and guiding the endotracheal tube by observation of the carbon dioxide (CO_2) waveform on a capnograph (5). Disadvantages of these methods include difficulty in hearing breath sounds and in observing condensation and exposure of the intubator to contamination with body secretions (especially occurring when the tube is passed into the glottis with an explosive cough). The need to look up at the CO_2 waveform may be a distraction at a time when concentration is most needed. Nevertheless, measurement of end-tidal CO_2 is the most reliable method for confirmation of endotracheal tube placement, and the use of audio-capnometry to guide the endotracheal tube eliminates the need to look up. This is based on the logical postulate that the concentration of CO_2 in the oropharynx is maximal over the glottis during expiration. Several blind nasotracheal intubations have been performed using an audio-capnometry intubation device, and the case report presented below describes our experience with this device.

Case Report

The audio-capnometry intubation device (Figure 1), which has not previously been described, was developed at Duke University Hospital. It consists of a Puritan Bennett Datex CO_2 monitor coupled to a voltage-controlled oscillator with a speaker. This yields an audible tone with a pitch that varies linearly with the concentration of CO_2. The Datex monitor was used as it has the least time lag compared with the Ohmeda and Novometrix CO_2 monitors. Detection of small changes in the concentration of CO_2 is facilitated by the use of an endotracheal tube with a

---

Received from Duke University Medical Center, Durham, North Carolina. Accepted for publication October 16, 1990.

Address correspondence to Dr. Omoigui, Department of Anesthesiology, L.S.U.M.C., 1501 King's Highway, Shreveport, LA 71130.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

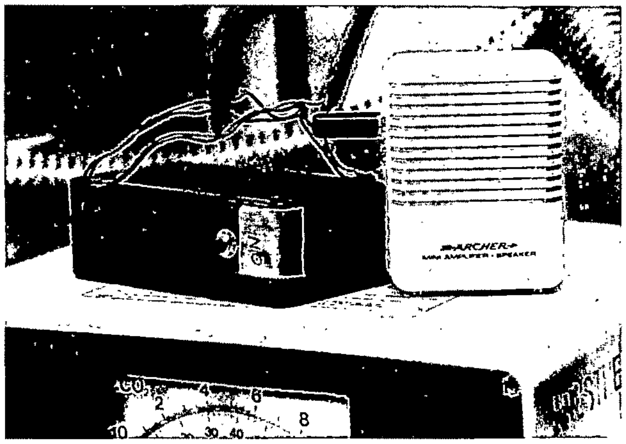


Figure 1. Audio-capnometry intubation device. It consists of a Puritan Bennett Datex CO_2 monitor coupled to a voltage-controlled oscillator with a speaker.

gas sampling port at the tip as with the Portex Blue line tracheal tube for gas monitoring (Concord/ Portex, Keene, N.H., Ref: 100198/080).

A 62-yr-old white woman after coronary artery bypass surgery developed increasing respiratory distress while in the acute care unit. Arterial blood gas tensions with an F_{IO_2} of 0.5 by face mask were pH 7.24, P_{O_2} 62 mm Hg, P_{CO_2} 51 mm Hg, and Sa_{O_2} 86.4%. Respiratory rate was 40 breaths/min and heart rate was 90 beats/min. There were occasional premature ventricular complexes recorded on the electrocardiogram. Because of incipient respiratory failure, mechanical ventilation via an endotracheal tube was indicated, and an awake nasal intubation was planned. Oxygen (100%) was then administered by face mask, which resulted in an oxygen saturation by pulse oximeter of 97%. After topicalization of the nasal mucosa with Cetacaine, a well-lubricated 8.0-mm Portex Blue Line Gas monitoring tracheal tube (Ref: 100198/080) with the CO_2 sampling port attached to the audible capnograph was inserted in the left nostril. The audio-capnometry intubation device was turned on, and as the tube was advanced, changes in pitch were heard in synchrony with the patient's respirations. The pitch suddenly decreased, and the patient was then noted to have bradycardia. Oxygen saturation was 95%. The endotracheal tube was withdrawn by a few centimeters. The heart rate returned to normal and the tube was readvanced while listening to the pitch of the sound. As the tube was advanced to the 25-cm mark, an oscillating high pitch was constantly heard despite difficulty in hearing air movement out of the endotracheal tube. The cuff was inflated and verification of tube placement was confirmed by visual CO_2 monitor, the presence of bilateral breath sounds, and ultimately, by chest x-ray. Vital signs were stable with oxygen saturation of 99%. Time for intubation was less than 3 min.

Discussion

The above case report illustrates the usefulness of audio-capnometry to guide blind nasotracheal intubation. Hearing a high pitch assures the user that the endotracheal tube is within the vicinity of the glottis. A sudden decrease in the pitch alerts the user that the endotracheal tube is being misdirected away from the glottis and allows for immediate correction. In the case report the decrease in pitch preceded the signs of vagal stimulation and prevented esophageal intubation. The audio-capnometry intubation device allows the user another method of guiding the endotracheal tube in blind nasal intubations without sole reliance on breath sounds.

The user can concentrate on the procedure with minimal risks of contamination by body secretions. It confirms immediately appropriate placement of the endotracheal tube. Secretions and blood interfere less with this technique than with fiberoptic bronchoscopy. Furthermore, oxygen can be provided through the nasotracheal tube during the procedure, whereas in the fiberoptic scope, oxygen is provided through the suction port. Conceivably, it could be adapted with fiberoptic bronchoscopy or could be used during anesthesia as a substitute for visual waveforms.

A potential problem in the design of the Portex tube is that excessive secretions may be suctioned into the CO_2 monitoring line, plugging it and causing a falsely low CO_2 tone to be emitted, thus necessitating verification of tube placement by another method. Furthermore, the device needs to be improved to increase its sensitivity to small changes in CO_2 concentration. Despite these limitations, audio-capnometry offers a distinct advantage during the performance of blind nasotracheal intubation. The device required is simple and easily assembled.

References

1. Shapiro H, Unger R. Blind, but not deaf or dirty, intubations. Anesthesiology 1986;64:297.
2. Gorback M. Inflation of the endotracheal tube cuff as an aid to blind nasal endotracheal intubation. Anesth Analg 1987;66:916–7.
3. Meyer R. Suction catheter to facilitate blind nasal intubation. Anesth Analg 1989;68:701.
4. Patil VL, Stehling L, Zauder H, Chilcoat R. An aid to blind endotracheal intubation. Anesth Analg 1984;65:882.
5. King H, Wooten D. Blind nasal intubation by monitoring end tidal CO_2. Anesth Analg 1989;69:412–3.

Onset of Amputation Stump Pain Associated With Epidural Anesthesia

Eisso R. Bulder, MD, and Willem L. H. Smelt, MD, PhD

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—onset of pain during. PAIN, AMPUTATION STUMP PAIN—during epidural anesthesia.

The acute onset of pain in lower extremity amputation stumps precipitated by spinal anesthesia has been reported (1–3). In this clinical report, a case of spontaneous onset of pain associated with epidural anesthesia in a 22-yr-old woman with a lower extremity amputation is described and a possible explanation for this phenomenon is proposed.

Case Report

A 22-yr-old woman was scheduled for split-thickness skin grafting of the stump and revision of the stump under epidural anesthesia 1 mo after a traumatic amputation of the right leg just below the knee. A similar procedure had been performed uneventfully 2 wk previously. Intravenous hydration with a Ringer's lactate solution was started after the blood pressure was measured using a sphygmomanometer. The electrocardiogram was continuously monitored.

With the patient lying on the left side and after the epidural space was identified using the loss-of-resistance technique with liquid, a catheter (Perifix G18, Braun, Helsungen, Germany) was inserted at the L3-4 interspace for a distance of 3 cm without encountering any significant resistance. There were no paresthesias. Two milliliters of 2% mepivacaine with epinephrine 1:200,000 was then injected through the catheter. After 3 min, an additional 14 mL of the same solution was administered after checking for signs or symptoms that might suggest either intravascular or subarachnoid injection.

As the anesthetic began to take effect, the patient complained of the acute onset of pain. The pain was located on the inferior aspect of the stump; it had a throbbing quality and was likened to a warm continuous electrical current. This pain was not present before the epidural anesthesia had begun to take effect and was not precipitated nor intensified by touching or manipulating the limb. The anesthesia eventually reached a level of L-2 with a Bromage level 1 of muscle paralysis (4).

In the belief that the anesthesia was pharmacologically incomplete, an additional dose of 10 mL of 1% lidocaine was injected through the catheter. The pain subsided after a few minutes, and the operation was carried out as planned with excellent anesthesia during the operation. Conversation during the operation with the patient revealed that she had experienced the same pain 2 wk before as the epidural anesthesia wore off. A 500-mg Naprosyn (naproxen) suppository had been given but this had had no effect on the pain.

At the conclusion of the present operation, which lasted 2.5 h, the patient experienced exactly the same pain as the anesthetic effect of the epidural began to wear off. Transcutaneous electrical nerve stimulation (Neuromod Dual-Channel, Medtronic, Del-Mar, Calif.) was used paravertebrally (L3-5) on the right side for a period of 30 min resulting in a definite regression of the pain, although it did not eliminate the pain completely.

Three and a half hours after the acute onset, the pain had totally worn off although she continued to feel a smarting pain above the right knee in the area where the skin graft had been taken. The stump pain did not recur.

Received from the Institute of Anaesthesiology, University Hospital Utrecht, Utrecht, and the Department of Anaesthesiology, Hospital "de Weezenlanden," Zwolle, The Netherlands. Accepted for publication October 24, 1990.

Address correspondence to Dr. Bulder, Institute of Anaesthesiology, University Hospital Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Discussion

The appearance of spontaneous pain after nerve lesions is a well-known phenomenon that has been reported several times (5,6). A possible explanation can be found in the gate-control theory of Melzack and Wall (5). The gate-control theory is based on three suppositions. First, afferent nerve fibers are composed of two subtypes, large- and small-diameter fibers with low and high thresholds, respectively, for external stimulation. Second, these two subtypes converge in the substantia gelatinosa of the dorsal horn where the large-diameter fibers inhibit the transmission of impulses of the small-diameter fibers to the central (pain) pathways. This inhibition is primarily presynaptic and is only counteracted by a disproportionate level of small-diameter fiber activity (nociception) that can lead to the perception of pain. This interaction is called the gate-control system. Finally, the site of the spinal gating mechanism is influenced by the descending central pathways from the brain. In this way, it is possible that certain types of central nervous system activity can exert control over pain perception. Cells in the gray matter around the aqueduct in the mesencephalon are important transmission stations in this action.

An explanation for the occurrence of spontaneous pain in cases similar to this one is given by Melzack in his article on summation mechanisms (6). The open gate produced by the predominantly small-diameter fiber input caused, for example, by a major loss of large peripheral nerve fibers, would provide the conditions for spatial and temporal summation of afferent impulses. In the absence of inhibitory control after the initial central transmission cell discharge, successive stimuli would produce a more intense and prolonged barrage of nerve impulses. These mechanisms may account for the fact that nonnoxious stimuli can trigger severe pain, as seen in patients suffering from phantom limb pain, causalgia, and certain neuralgias.

Spontaneous pain, which occurs in the absence of any obvious stimulation, can also be explained in terms of summation mechanisms. The spontaneous activity generated by the remaining small-diameter fibers after a nerve lesion would have the effect of keeping the gate open. Low-level, random, ongoing activity would then be transmitted relatively unchecked and the summation of these impulses would produce spontaneous pain. Thus, where there is only spontaneous activity generated by the small-diameter fibers, the gate will be temporarily opened or kept open and this can, by the summation of impulses, produce pain.

Another important observation is that during the onset of epidural anesthesia, transmission of impulses by nerve fibers in the epidural space is still possible not only in the large-diameter fibers but also in the small-diameter fibers (7,8). Sprotte described this possibility by noting that the cold reflex with its afferent transmission of impulses through weakly myelinated A δ-fibers and its efferent transmission through nonmyelinated C fibers is not always blocked before voluntary somatic motor function (7). This is true in both epidural anesthesia and peripheral nerve blocks. Pain fibers, which are myelinated A δ-fibers and C fibers, are morphologically identical to the nerve fibers making up the afferent and efferent pathways, respectively, of the cold reflex. There is no morphologic support for differential sensitivity of pain fibers so that there is always the possibility of perception of pain and conduction of pain impulses during the onset of epidural anesthesia. An important corollary to this is that the blockade of transmission of impulses along nerve fibers by local anesthesia may not be equated with loss of perception.

Another observation that points to the possibility of continued transmission of impulses by small-diameter fibers under these circumstances appears in a paper by Gissen et al. (8). In that paper, it was suggested that by manipulating factors such as the type and concentration of local anesthetic and the duration of nerve exposure to the local anesthetic in isolated nerve experiments, it is possible to have A, B, or C fibers more profoundly and more rapidly blocked than other fibers. This capacity for differential blockade may result in differing effects on sensory and motor functions. This line of reasoning suggests that, during the onset and regression of epidural anesthesia, it is possible there may still be spontaneous activity generated by small-diameter afferent fibers coming from an area where a peripheral nerve has been injured when the large-diameter fibers from the same area are already blocked. In this way, the gate will be opened and spontaneous pain will be perceived. When the blockade is complete, the gate will be closed because the small-diameter fibers are also blocked. After the blockade has totally worn off, the gate will again be closed because the large-diameter fibers will inhibit the transmission of impulses from the small-diameter fibers to the central ascending pathways.

The favorable influence of transcutaneous electrical nerve stimulation on the pain experienced by our patient is also explicable in terms of the gate-control theory (9). The large myelinated A fibers have a lower threshold for electrical stimulation than the smaller unmyelinated C fibers and the A δ-fibers. Stimulation of the large myelinated A fibers with transcutaneous electrical nerve stimulation, therefore, inhibits the transmission of pain impulses carried by the smaller A δ-fibers and C fibers. This inhibition takes place at the level of the spinal cord in the substantia gelatinosa of the dorsal horn and in the higher central nervous system. When the large-diameter fibers are partially blocked, the influence of transcutaneous electrical nerve stimulation might be less evident.

In summary, patients with peripheral nerve damage can perceive acute pain during the onset and regression of epidural anesthesia. An explanation can be found in the gate-control and summation theory of Melzack and Wall and in the concept of differential block.

We thank D. T. Bolton, MB, ChB, DObst RCOG, FFARCS, for review of the manuscript and valuable commentary.

References

1. Davis T. Spinal analgesia. Anesthesiology 1958;19:682–3.
2. Harrison G. Phantom limb pain occurring during spinal analgesia. Anaesthesia 1951;6:114–6.
3. Leatherdale RAL. Phantom limb pain associated with spinal analgesia. Anaesthesia 1956;11:249–51.
4. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anaesthesiol Scand 1965;9(Suppl 16):55–69.
5. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.
6. Melzack R. The puzzle of pain. Middlesex, UK: Penguin Books, 1973:170–2.
7. Sprotte G. Thermographic investigations into the physiological basis of regional anaesthesia. Berlin and Heidelberg:Springer-Verlag, 1985:8–40.
8. Gissen AJ, Covino BG, Gregus J. Differential sensitivity of fast and slow fibers in mammalian nerve. II. Margin of safety for nerve transmission. Anesth Analg 1982;61:561–9.
9. Raj P. Practical management of pain. Chicago and London: Year Book Medical Publishers, 1986:783–95.

Speedballs: A New Cause of Intraoperative Tachycardia and Hypertension

Jon Samuels, MD, Steven S. Schwalbe, MD, and Gertie F. Marx, MD

Key Words: ANESTHETICS, LOCAL—cocaine. COMPLICATIONS—cocaine self-administration.

Various events occurring during otherwise uneventful general anesthesia can result in tachycardia and hypertension. We report a case in which such a response resulted from the patient's self-administered premedication.

Case Report

A 27-yr-old man presented electively for closure of a colostomy that had been performed 3 mo earlier after a gunshot wound to the abdomen. He admitted to previous intravenous cocaine use but denied any such injection since his injury. Physical examination and laboratory values were within normal limits except for old "track marks" in both antecubital fossae and a hematocrit of 31%.

Before transport to the operating room, an intravenous infusion of 5% dextrose in lactated Ringer's solution was started and 75 mg meperidine and 75 mg hydroxyzine were injected intramuscularly. The patient appeared calm on arrival in the operating room with a blood pressure (BP) of 128/78 mm Hg and a heart rate (HR) of 92 beats/min. After placement of the required monitors, anesthesia was induced with 5 mg midazolam in divided doses, 50 μg fentanyl, and 400 mg (5 mg/kg) thiamylal. Orotracheal intubation was performed easily after injection of succinylcholine, and tube position was confirmed by auscultation and capnography. Anesthesia was continued with 60%/40% nitrous oxide/oxygen and isoflurane (1–2 vol%); vecuronium was used for muscle relaxation. Twenty minutes after induction, HR began to increase steadily with maintained regular sinus rhythm. The pupils were midsize. Although the depth of anesthesia seemed adequate, 50 μg fentanyl was injected and the concentration of isoflurane increased but without improvement. An arterial blood sample revealed no noteworthy decline in hematocrit (28%) and no acid-base imbalance (base deficit 2.1). The temperature was 36°C. Review of the hospital chart confirmed normal thyroid function tests. At this time, 20 min after the beginning of tachycardia, BP started to increase as well. The Foley catheter showed adequate drainage and palpation of the urinary bladder by the surgeon revealed no overdistention. Fiberoptic examination ruled out irritation of the carina by the tip of the endotracheal tube. Heart rate remained at 132 beats/min, but BP increased to 160/100 mm Hg. Unknown drug intake became suspect. Three intravenous doses of 10 mg labetalol were administered. Heart rate decreased to 94 beats/min and BP to 130/86 mm Hg. At the completion of surgery, muscle relaxation was not reversed. The endotracheal tube was removed 4.5 h after insertion with the patient breathing well at 24 breaths/min, BP 130/90 mm Hg, and HR 100 beats/min. During the postanesthetic visit 24 h later, the patient reluctantly admitted to having injected two "speedballs" into the intravenous infusion shortly before being transported to the operating room.

Discussion

Speedball is a street name for heroin laced with cocaine. It combines the initial high "kick" of cocaine with the subsequent euphoric sleep "rush" of heroin. The relatively pure drug mixture may be "cut" with various substances, such as sugars, local anesthetics, caffeine, amphetamines, phencyclidine, and quinine. Cocaine is an alkaloid stimulant and local anesthetic extracted from the leaves of the coca plant present as

---

Received from the Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, New York. Accepted for publication October 25, 1990.

Address correspondence to Dr. Schwalbe, Department of Anesthesiology, Albert Einstein College of Medicine, Jacobi Hospital—Room 1226, Pelham Parkway and Eastchester Road, Bronx, NY 10461.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

a hydrochloric salt. Heroin is a semisynthetic opioid analgesic extracted from the seeds of the poppy plant. The mixture is a fine white powder that is most frequently injected, although it is readily absorbed by any route (1,2). Cocaine onset occurs in approximately 11 min and has an elimination half-life of 78 min (3). The reuptake of norepinephrine and dopamine is blocked at the nerve terminals, causing excess catecholamines to accumulate at postsynaptic receptor sites. This results in intense sympathetic stimulation, both centrally and peripherally. Characteristic signs and symptoms of acute cocaine toxicity include restlessness, nausea and vomiting, mydriasis, increased HR, and hypertension (4). MAC_{BAR} (5), the concentration of potent inhalation anesthetics needed to blunt a hyperdynamic cardiovascular response, is also increased. With chronic high-dose intake of the substance, irregular breathing, chest pain, cardiac dysrhythmias, and hypotension develop (4). Heroin works centrally on opioid receptors as a μ_1-agonist. Signs of heroin onset are masked by cocaine but, by 1.5 h after injection, respiratory depression, decreased HR, decreased MAC, and miosis supervene (2). Duration of action is approximately 3–4 h. If general anesthesia is discontinued before 4 h, the patient may be stuporous. Naloxone is contraindicated as it may precipitate acute narcotic withdrawal and induce pulmonary edema and ventricular dysrhythmias in the presence of residual cocaine (6). Rather, the patient should be allowed to awaken slowly, employing mechanical ventilation as long as necessary.

Treatment of acute cocaine toxicity depends on the severity of the symptoms. Mild cardiovascular reactions require only supportive care. Hypertension and dysrhythmias may be treated with β-blockers (propranolol, labetalol, esmolol) or with calcium channel blockers. Labetalol is preferred in the presence of hypertension because propranolol is associated with α-adrenergic stimulation. The calcium moderator nitrendipine (7) appears to have general protective effects against cocaine cardiac toxicity and may be the optimal therapy for ventricular dysrhythmias.

In conclusion, anesthesiologists must recognize the possibility of preoperative self-administration of illicit substances by anxious drug-dependent patients and must include this possibility in the differential diagnosis of unexplained intraoperative tachycardia and hypertension. The use of infusion tubing without injection ports until arrival in the operating room may help prevent intravenous administration. However, it has been our experience that patients will find ingenious ways to obtain and take these substances. The anesthesiologist must therefore maintain a high index of suspicion in order to make the proper diagnosis.

References

1. Ritchie JM, Green NM. Local anesthetics. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's the pharmacological basis of therapeutics, (7th ed). New York: Macmillan, 1985:302–21.
2. Jaffe JH, Martin WR. Opioid analgesics and agonists. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. Goodman and Gilman's the pharmacological basis of therapeutics, 7th ed. New York: Macmillan, 1985:491–531.
3. Jeffcoat AR, Pere-Reyes M, Hill JM, Sadler BM, Cook CE. Cocaine disposition in humans after intravenous injection, nasal insufflation (snorting) or smoking. Drug Metab Dispos 1989;17:153–9.
4. Gradman AH. Cardiac effects of cocaine: a review. Yale J Biol Med 1988;61:137–47.
5. Stevens WC, Kingston HG. Inhalation anesthesia. In: Barash PG, Cullen BF, Stoelting RK, eds. Clinical anesthesia. Philadelphia: Lippincott, 1989:308–10.
6. Kissner DG, Lawrence WD, Selis JE, Flint A. Crack lung: pulmonary disease caused by cocaine abuse. Am Rev Respir Dis 1987;136:1250–2.
7. Trouve R, Nahas G. Nitrendipine: an antidote to cardiac and lethal toxicity of cocaine. Proc Soc Exp Biol Med 1986;183:392–7.

ANESTH ANALG 1991;72:399–403

Are Breech Deliveries an Indication for Lumbar Epidural Analgesia?

Andre Van Zundert, MD, PhD, Leo Vaes, MD, Maurice Soetens, MD, Marc De Vel, MD, Paul Van Der Aa, MD, Agnes Van Der Donck, MD, Herman Meeuwis, MD, and Francis Smolders, MD

Key Words: ANESTHESIA, OBSTETRIC—breech deliveries. ANESTHETICS, LOCAL—bupivacaine. ANESTHETIC TECHNIQUES, EPIDURAL—breech deliveries.

Lumbar epidural analgesia (LEA) for pain relief in labor and delivery is still considered to reduce expulsion forces, thereby prolonging the second stage of labor and increasing the number of instrumental deliveries (1–4).

The second stage of labor has been regarded as a time of particular risk for the development of fetal hypoxia, as reflected by the progressive deterioration in acid-base status of the fetus during the expulsion phase (5). The duration of the second stage of labor also adversely affects the neonatal acid-base balance (6,7). Kalinkov et al. (8) found that expulsion phases lasting more than 20–30 min produce metabolic acidosis due to production of lactate during maternal straining. Labor with a second stage lasting longer than 120 min is associated with increased perinatal mortality (9–11).

All the above is of special concern in breech deliveries to such an extent that some obstetricians hesitate and even refuse to use LEA for breech deliveries (12–15).

In an earlier study, we demonstrated in 877 singleton vertex deliveries that an LEA technique using 0.125% bupivacaine plus epinephrine 1:800,000 led to a mean expulsion time of 6.80 ± 0.15 min (16).

In our institution, vaginal breech deliveries are considered by the obstetricians as a strong indication for LEA. In this survey, we studied the duration of the second stage, the expulsion times (ETs), the instrumental delivery rate, and the condition of the newborns in 165 breech presentations receiving LEA using the same low dose-low concentration bupivacaine technique.

Materials and Methods

We examined anesthesia and obstetrical charts of 15,145 deliveries for a 10-yr period (from January 1979 to January 1989) to identify the patients who had breech deliveries.

The epidural space between L-3 and L-4 was located with the Dogliotti loss-of-resistance technique, and a catheter (Portex 100/380/300) was introduced. Analgesia with 0.125% bupivacaine + epinephrine 1:800,000 was started as soon as labor was established and the parturient asked for pain relief, regardless of the dilatation of the cervix. Analgesia was maintained by intermittent injections of the same local anesthetic solution. The level of sensory block was determined by pinprick. Assessment of quality of analgesia was made by using the following scoring system: excellent (when the mother was completely free of pain from the first or the second injection till the end of delivery); good (when the mother was satisfied despite some pain being experienced for a short period during labor or delivery); incomplete (when the woman had significant pain relief but experienced some pain during most of labor and delivery); and failure (when, after the start of epidural analgesia, pain was experienced throughout labor and delivery). No attempt was made to preserve the bearing-down reflex. On the contrary, an extra dose was given in the sitting position if the perineum was not perfectly anesthetized. When the obstetrician decided that the woman was ready for delivery, she was transferred to the delivery room and instructed to begin with the expulsive efforts.

Received from the Department of Anesthesia and Reanimation, St.-Elisabeth Hospital, Turnhout, Belgium. Accepted for publication October 29, 1990.

Address correspondence to Dr. Van Zundert, Kempenlaan 12, 2300 Turnhout, Belgium.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Types of Deliveries in 554 Patients With Breech Presentations

			Trial of labor	
	n	%	Epidural	Non-epidural
Primary cesarean section	201	36.3	—	—
Secondary cesarean section	70	12.6	62	8
Vaginal delivery	283	51.1	219	64
Total	554	100	281	72

Maternal age, weight, and height, parity, cervical dilatation at the start of analgesia, quality of analgesia, highest level of sensory blockade, duration of analgesia, total dose of local anesthetic, duration of the second stage, ET, weight of the newborn, 1- and 5-min Apgar scores, and resuscitation methods were recorded. "Expulsion time" was defined as the time from the first expulsion effort by the mother to the delivery of the baby.

Statistical analysis was performed using the analysis of variance for repeated measures. All results are expressed as mean ± SEM. $P < 0.05$ was considered to be statistically significant.

Results

Of 15,145 deliveries in a 10-yr period, 554 (3.66%) were singleton breech presentations (Table 1). Of these, 201 (36.3%) had a primary cesarean section. Seventy-two women did not request LEA. A trial of labor under epidural analgesia was started in 281 parturients, of which 62 (22%) had a secondary cesarean section for lack of progress of dilatation (79%) or for failure of descent (21%). Of the 219 vaginal breech deliveries under epidural analgesia, 54 were not included in the study for the following reasons: 9 women delivered so fast that no analgesia could be obtained; 6 babies had a low birth weight (<1900 g); in 18 women mixtures of local anesthetics or high concentrations of local anesthetics were used; and in 21 files essential data (second stage, ET) were not mentioned.

Of the remaining 165 breech deliveries under LEA, 55% were primigravidae. The estimated fetal weight was always between 2000 and 4000 g and the estimated fetal age was beyond 36 wk. Labor was induced in 39%, using oxytocics (Syntocinon, Sandoz) or prostaglandin tablets (Prostin E2). Another 43% received Syntocinon in a dose of between 1 and 8 mU/min to stimulate labor. Cardiotocographic monitoring was performed in all cases.

Table 2. Demographic Data in 165 Patients Having Breech Deliveries

	Mean	SEM	Median	Range
Maternal age (yr)	26	0.3	25	16–35
Maternal weight (kg)	68	0.7	68	47–116
Maternal height (cm)	165	0.8	165	152–178
Cervical dilatation at start of epidural block (cm)	4.3	0.1	4	1–9
Duration of epidural analgesia (min)	273	13.2	240	30–880
Total dose of bupivacaine (mg)	61	1.7	56	25–155
Duration of the second stage (min)	30.9	1.2	27	8–90
Expulsion time (min)	8.7	0.4	8	1–40
Baby's weight (g)	3148	32.5	3150	1960–4050

For the 165 vaginal breech deliveries in this study, data were available on maternal age, weight, and height, cervical dilatation at the start of analgesia, duration of analgesia, total dose of bupivacaine, duration of the second stage, ET, and weight of the baby (Table 2 and Figures 1 and 2). In all 165 parturients a sensory level of analgesia to T-10 was obtained, but in 7.7% a maximum sensory level above T-6 was seen. During the first stage of labor, analgesia was excellent or good except for one "failure," which needed a new catheter, and four "incomplete," as judged by the mother or the anesthesiologist. In 71% ($n = 131$) of all deliveries an additional injection of bupivacaine in the sitting position was given, which resulted in excellent perineal anesthesia in all but three women: in two women expulsion was so fast that even local perineal infiltration could not be performed. In the third woman the sensory block did not include the sacral segments and a local infiltration provided her with a pain-free delivery. Pudendal blocks were never used in this series. A mean total dose of 61 ± 1.74 mg of bupivacaine was administered for a mean duration of epidural analgesia of 273 ± 13.22 min.

The mean duration of the second stage in these 165 vaginal breech deliveries was 30.86 ± 1.21 min (range, 8–90 min). The mean ET was 8.7 ± 0.44 min (range, 1–40 min). In primigravida the mean ET of 9.7 ± 0.66 min was significantly longer ($P < 0.05$) than in multigravidae (7.7 ± 0.56 min). The ET exceeded 20 min in four women: three primigravidae

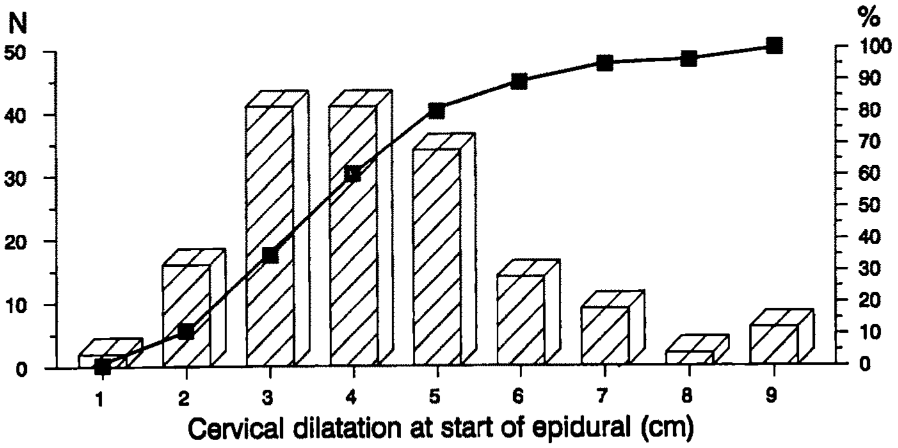


Figure 1. Frequency (*n, hatched bars*) and cumulative incidence (%, -■-) of cervical dilatation at the start of the first epidural injection in 165 breech deliveries.

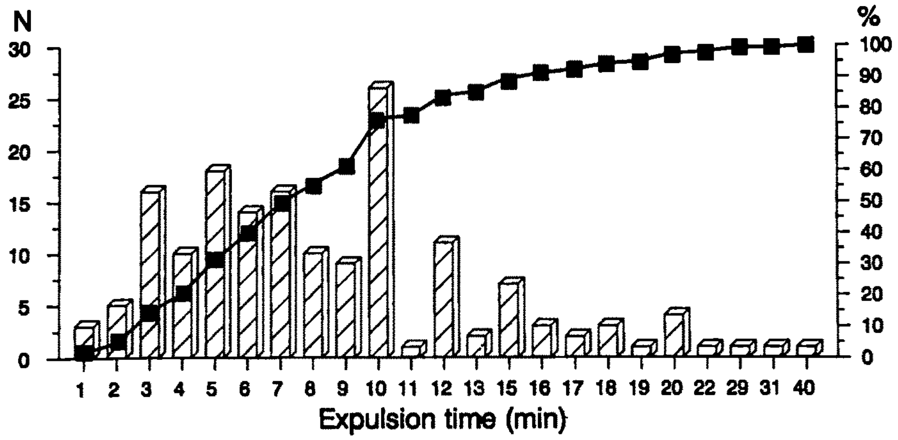


Figure 2. Frequency (*n, hatched bars*) and cumulative incidence (%, -■-) of ET in 165 breech deliveries.

(22 min, 29 min, and 31 min, with baby weights of 3150 g, 3700 g, and 2450 g, and Apgar scores of 6–8, 7–9, and 5–9, respectively) and one secundogravida (ET of 40 min, baby weight of 3400 g, Apgar score 6–7) (Figure 2).

The seven babies with a birth weight of less than 2500 g (range, 1960–2450 g) in these 165 cases were delivered after a mean ET of 8 min (range, 1–29 min). Twenty babies had a weight over 3600 g (range, 3650–4050 g) with a mean ET of 11.8 min (range, 5–31 min).

In 10 of the 165 patients instrumental assistance was used for delivery: twice low forceps were used for delivery of the aftercoming head, and eight times a soft cup vacuum extractor was applied to the presenting part of the breech delivery (Table 3). The mode of delivery, whether instrumental or not, did not influence the ET: the mean ET was 9.7 ± 1.34 min in instrumentally delivered babies and 8.6 ± 0.46 min in spontaneously delivered babies ($P > 0.05$). There was no significant difference ($P > 0.05$) between the ETs in the cases handled by the eight attending obstetricians (Table 4), although one obstetrician performed 8 of the 10 instrumental deliveries.

Table 3. Mode of Vaginal Delivery in 165 Breech Births and the Corresponding Expulsion Times

			Expulsion time		
Mode of delivery	*n*	%	Mean	SEM	*P* value
Instrumental	10	6	9.7	1.3	
Spontaneous	155	94	8.6	0.5	
Total	165	100	8.7	0.4	>0.05

The obstetricians who used a strict Bracht's maneuver, in which the infant is extruded spontaneously as far as the umbilicus, had ETs no longer ($P > 0.05$) than those of obstetricians who occasionally intervened by early manipulative or instrumental assistance (8.9 vs 8.6 min). In patients of the obstetrician who used a soft cup vacuum extractor on the buttocks eight times, ET averaged 7.5 min.

One hundred twenty-six of the 165 breech babies (76%) had an Apgar score ≥7 at 1 min. At 5 min all

Table 4. Number of Deliveries, Mean Expulsion Times, and Number and Rate of Instrumental Deliveries for Each Obstetrician

	Deliveries		Expulsion time		Instrumental deliveries	
Obstetrician	*n*	%	Mean	SEM	*n*	%
1	7	4.2	7.9	1.2	0	—
2	35	21.2	7.1	0.7	0	—
3	43	26.1	9.8	0.9	1	2
4	19	11.5	7.7	1.0	0	—
5	22	13.3	8.5	1.4	1	5
6	8	4.8	13.8	4.3	0	—
7	17	10.3	9.6	1.1	0	—
8	14	8.5	7.5	1.2	8	57
Total	165	100	8.7	0.4	10	6

Table 5. Number of Babies With Apgar Scores Less Than 7

Apgar score	0	1	2	3	4	5	6	*n*	%
Vaginal breech deliveries (*n* = 165)									
At 1 min	—	4	7	5	5	7	11	39	23.6[a]
At 5 min	—	—	—	—	1	2	3	6	3.6[b]
Vaginal vertex deliveries (*n* = 165)									
At 1 min	—	3	2	1	1	3	8	18	10.9
At 5 min	—	1	—	—	—	1	2	4	2.4
Cesarean sections for breech birth (*n* = 165)									
At 1 min	—	2	0	5	1	2	7	17	10.3
At 5 min	—	—	—	—	—	2	2	4	2.4

[a] Statistically different versus vaginal vertex deliveries and cesarean sections.

[b] Not statistically significant versus vaginal vertex deliveries and cesarean sections.

but six babies (96%) had Apgar scores at 7 or more (Table 5). Each of these six babies had a 1-min score of less than 4. In one baby with Apgar scores of 1 and 5, no resuscitation efforts were made because of gross congenital malformations. The five other babies were given bicarbonate. All of the remaining 159 (96%) babies required only oxygen administration or needed no resuscitation at all after delivery. Table 5 also shows the 1- and 5-min Apgar scores of 165 singleton vertex deliveries under LEA and 165 cesarean sections for breeches under LEA.

Discussion

Prolonged second stages of labor are often mentioned as a disadvantage of LEA. Exact determination of the duration of the second stage is, however, difficult because it depends largely on the frequency of examination. Moreover, it is not proven that a prolonged second stage in itself is harmful to the baby, provided the ET is short. For these reasons, we think it is better to look at the ET, a more precise and relevant datum, than duration of the second stage.

It is important to avoid prolonged ET during which lactic acid accumulation and metabolic acidosis may develop (6–8,11). A mean ET of 8.7 ± 0.44 min in our 165 breech deliveries is comparable to our results in former studies (6.8 ± 0.15 min) in singleton vertex deliveries using the same epidural technique (16,17). A mean total dose of 61 ± 1.74 mg of bupivacaine was administered for a mean duration of epidural analgesia of 273 ± 13.22 min, which is 13.4 mg/h. This is quite a small dose when it is realized that 10% of the epidural administrations were started at a cervical dilatation of 1–2 cm and that an additional 50% started at 3–4 cm.

In the present study we noticed that one obstetrician (obstetrician 8) had a high soft-cup vacuum extraction rate (57%). In a former study of 877 vaginal deliveries under epidural analgesia, the same obstetrician had an instrumental delivery rate of 78% (16). However, the interesting point is that the average ET in his patients was not shorter than was that in patients delivered by other obstetricians (Table 4). Effective analgesia may tempt the obstetrician to perform an instrumental delivery rather than to wait for a spontaneous delivery.

Over two decades, there has developed a trend toward more liberal cesarean section in many areas, especially in patients with breech presentations. Our obstetricians are convinced that selected patients with breech presentation should be offered a trial of vaginal delivery. In our opinion epidural analgesia with good perineal anesthesia is particularly indicated in vaginal breech deliveries. Premature expulsion efforts with the danger of cord prolapse and head entrapment are effectively prevented. A comfortable, cooperative parturient with a relaxed perineum allows, when necessary, a shortening of the umbilicus to head delivery interval and a controlled delivery of the aftercoming head (12,18).

This study has shown that LEA, given with intermittent doses of 0.125% bupivacaine plus epinephrine 1:800,000 in 165 breech deliveries, resulted in good neonatal conditions as evaluated by the 5-min Apgar scores. This agrees with the data of Gimovsky et al. (19) and Coltart (20) who found morbid Apgar scores (<7 at 5 min) in only 3% of breech babies. Our 5-min Apgar scores in breech deliveries are not different from Apgar scores in our group of vertex deliveries or cesarean sections for breech deliveries (Table 5). There are certainly more low 1-min Apgar scores in the vaginally delivered breech babies (Table 5). But does this difference justify a cesarean section? In a critical review, Myers and Gleicher failed to support the routine use of cesarean deliveries for all cases of breech delivery and suggested that the need for abdominal delivery should not exceed 20%–25% of all breech deliveries (21). Adding incremental doses of 10 μg of sufentanil (maximum, 30 μg) to our standard low dose-low concentration epidural technique in vertex deliveries further reduces the hourly dose of bupivacaine, improves the quality of analgesia, and reduces the incidence of instrumental delivery by one-third. Currently, we are investigating this technique for breech deliveries as well.

In conclusion, in both vertex and breech deliveries, ET under LEA can be short, despite adequate perineal analgesia during the expulsion phase. The myth that a correctly managed epidural analgesia technique prolongs the ET and increases the instrumental delivery rate should come to an end. We plead for use of ET instead of the duration of the second stage when evaluating the efficiency and usefulness of different types of analgesia in obstetrics.

We gratefully acknowledge the assistance of Dr. H. H. M. Korsten in the analysis of the data.

References

1. Bates RG, Helm CW. Uterine activity in the second stage of labour and the effect of epidural analgesia. Br J Obstet Gynaecol 1985;92:1246–50.
2. Chestnut DHF, Vandewalker GE, Owen CL, Bates JN, Choi WW. The influence of continuous epidural bupivacaine analgesia on the second stage of labor and method of delivery in nulliparous women. Anesthesiology 1987;66:774–80.
3. Kaminsky HM, Stafl A, Aiman J. The effect of epidural analgesia on the frequency of instrumental obstetric delivery. Obstet Gynecol 1987;69:770–3.
4. Bailey PW. Epidural anaesthesia and instrumental delivery. Anaesthesia 1989;44:171–2.
5. Wood C, Ng KH, Hounslow D, Benning H. The influence of difference of birth times upon fetal condition in normal deliveries. J Obstet Gynaecol Br Commonw 1973;80:289–94.
6. Zador G, Nilsson BA. Low intermittent epidural anaesthesia with lidocaine for vaginal delivery. II. Influence on labour and foetal acid-base status. Acta Obstet Gynecol Scand Suppl 1974;34:17–30.
7. Livnat E, Fejgin M, Scommegna A, Bieniarz J, Burd L. Neonatal acid-base balance in spontaneous and instrumental vaginal deliveries. Obstet Gynecol 1978;52:549–51.
8. Kalinkov D, Schachinger H, Buchholz R. Quelle est la durée tolérable de la phase d'expulsion foetale? Rev Fr Gynécol 1980;75:357–61.
9. Butler NB, Bonham DG. Perinatal mortality. The first report of the 1958 British Perinatal Mortality Survey. Edinburgh: Livingstone, 1963.
10. Döring GK, Kraus V, Über die Bedeutung der Geburtsdauer für das Kind. Geburtshilfe Frauenheilkd 1967;27:1185.
11. Niswander KR, Gordon M, eds. The women and their pregnancies. Washington, DC: U.S. Department of Health, Education and Welfare, Publication No. (NIH) 73-379, 1972.
12. Bowen-Simpkins P, Fergusson ILC. Lumbar epidural block and the breech presentation. Br J Anaesth 1974;46:420–4.
13. Breeson AJ, Kovacs GT, Pickles BG, Hill JG. Extradural analgesia—the preferred method of analgesia for vaginal breech delivery. Br J Anaesth 1978;50:1227–30.
14. Rolly G. Critical evaluation of epidural analgesia in obstetrics. Acta Anaesthesiol Belg 1981;32:277–81.
15. Brownridge P. A three year survey of an obstetric epidural service with top-up doses administered by midwives. Anaesth Intens Care 1982;10:298–308.
16. Van Zundert A, Van Der Aa P, Van Der Donck A, Meeuwis H, Vaes L. Motor blockade, expulsion times and instrumental deliveries associated with epidural analgesia for vaginal delivery. Obstet Anesth Digest 1984;4:152–6.
17. Van Zundert A, Burm A, Van Kleef J, et al. Plasma concentrations of epidural bupivacaine in mother and newborn: 0.125% versus 0.375%. Anesth Analg 1987;66:435–41.
18. Crawford JS. An appraisal of lumbar epidural blockade in patients with a singleton fetus presenting by the breech. J Obstet Gynaecol Br Commonw 1974;81:867–72.
19. Gimovsky ML, Petrie RH, Todd WD. Neonatal performance of the selected breech vaginal delivery. Obstet Gynecol 1980;56:687–91.
20. Coltart TM. Management of breech presentation. Br J Hosp Med 1983;29:45–9.
21. Myers SA, Gleicher N. Breech delivery: why the dilemma? Am J Obstet Gynecol 1986;155:6–10.

Nightmares and Recovery From Anesthesia

D. Suresh, MBBS, DA, FFARCSI

Key Words: ANESTHETICS, INTRAVENOUS—propofol. COMPLICATIONS, NIGHTMARES—during recovery.

Several postoperative sequelae have been reported after outpatient anesthesia (1). The more recent reports involve the recently introduced propofol, which fulfills many of the requirements of an induction agent for this type of surgery. Dreaming in particular seems to be quite common, with arousal from anesthesia reported as being generally pleasant and sometimes even erotic (2,3). There is no record in the literature, however, of a patient experiencing a habitual nightmare during emergence from general anesthesia.

Case Report

A 27-yr-old nurse, ASA physical status I, was admitted for removal of a contraceptive coil as a day-stay patient. She had no history of asthma, psychiatric disorder, epilepsy, or other neurological disorders. General anesthesia elsewhere for insertion of the coil 2 yr previously was uneventful.

Anesthesia was induced with 130 mg propofol and maintained with 2% isoflurane and 65% nitrous oxide in oxygen at a flow rate of 9 L/min using a Bain system and a face mask. The procedure was completed uneventfully and lasted 6 min, with the patient waking as she was wheeled into the recovery area. A few minutes later her breathing became increasingly labored, with marked inspiratory stridor, which sounded rather "pharyngeal." A striking feature was that her neck muscles anteriorly were extremely taut. All possible maneuvers to maintain a clear airway failed to improve the symptom. Oddly, despite the general impression of near total obstruction and apparent difficulty in supporting ventilation, her color remained good, with pulse oximetry indicating normal saturation. She was turned onto her side. No evidence of either bronchospasm or regurgitation could be found. After intravenous atropine and the warning that she would feel weak, 20 mg succinylcholine and 50% nitrous oxide in oxygen allowed easy ventilation and provided a clear airway for resumption of spontaneous respiration. This time, identical symptoms were accompanied by odd jerking movements of the entire body, with the patient now clutching her throat with her right hand in the classic "cafe coronary" manner and raising the possibility of persisting mechanical obstruction. To confuse the issue further, the scrub nurse, a distant relative of the patient, volunteered the information that the patient's sister had epilepsy.

Laryngoscopy after thiopental and succinylcholine was entirely normal, with no physical or mechanical cause to account for the symptoms and signs of airway obstruction. Recurrence of these with hyperventilation after extubation responded to 5% CO_2 in oxygen and 5 mg midazolam intravenously. For the next hour she needed repeated and firm reassurance that she was not "choking" before transfer to the ward for overnight observation.

A chat with the patient that evening proved most illuminating. Since the age of 11, she had suffered nightmares roughly 10 to 15 times a month, with the most recent one 3 days before her anesthetic. Characteristically, these always involved someone attempting to strangle her. Her spontaneous demonstration of these regular attempts on her life was quite fascinating in that it was absolutely identical to the manner in which she clutched her throat repeatedly during emergence. She could not however, recall dreaming or having a nightmare during this anesthetic.

Discussion

There was no history of attempts on this patient's life, and she denied sexual abuse or violence during

---

Received from the Department of Anaesthetics, The Royal London Hospital, London, United Kingdom. Accepted for publication November 9, 1990.

Address correspondence to Dr. Suresh, Anaesthetics Unit, The Royal London Hospital, Whitechapel E1 1BB, United Kingdom.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

childhood. She could not recall being told that she snores or wakes up fighting for her breath. She was also quite certain that what woke her up was the nightmare of strangulation and not any physical sensation of choking or suffocation. While she realized that suffering nightmares for roughly 7 yr was probably not normal, it was certainly not an indication for psychotherapy, as her 4-yr-old daughter had nightmares as well!

Uninhibited behavior, hallucinations, and opisthotonus have all been reported after anesthesia with propofol (3–6). That this patient's emergence might represent a further example of an unusual form of recovery attributable to propofol must remain conjectural and is possibly discounted by the persistence of symptoms after thiopental for laryngoscopy. Additionally, while this patient's presentation may superficially resemble and possibly be confused for opisthotonus, no extension of the neck or arching of the back was seen (5,6). Moreover, the unique history and the extremely taut neck muscles (as in someone resisting strangulation) point to an experience during emergence identical to her usual nightmares. This suggests that the nature of arousal after anesthesia is probably influenced by a patient's individual experiences and personality.

However, because dreaming is quite common after propofol anesthesia (2), it would be prudent either to avoid propofol, or at least to bear in mind the possibility of these peculiar patterns of recovery where such a history of unpleasant dreams or nightmares is elicited preoperatively. Patients with certain types of documented personality disorders would also justify a similarly cautious approach in their management.

References

1. Hindmarch I, Jones JG, Moss E, eds. Aspects of recovery from anaesthesia. New York: John Wiley & Sons, 1987:167–70.
2. Gunawardene RD. Propofol and dreaming. Anaesthesia 1989; 44:266–67.
3. Hunter DN, Thornily A, Whitburn R. Arousal from propofol. Anaesthesia 1987;42:1128–9.
4. Lloyd EL. Hallucinations after anaesthesia. Anaesthesia 1987; 42:1015–6.
5. Laycock GJA. Opisthotonus and propofol: a possible association. Anaesthesia 1988;43:257.
6. Saunders PRI, Harris MNE. Opisthotonus and other unusual postoperative neurological sequelae after outpatient anaesthesia. Anaesthesia 1990;45:552–7.

Letters to the Editor

The Importance of Documenting Complete Sympathetic Blockade

Key Words: PAIN, CAUSALGIA. SYMPATHETIC NERVOUS SYSTEM—diagnostic block.

To the Editor:

We believe the recent letters to the editor by Lee (1) and de Jong (2) deserve amplification. We agree with de Jong that the implication of the title of the clinical report by Cicala et al., "Causalgic Pain Responding to Epidural but Not to Sympathetic Nerve Blockade" (3), may not tell the complete story. This report describes a patient who sustained a gunshot wound to the abdomen with a resultant incomplete lumbosacral plexus injury and signs and symptoms consistent with a causalgia involving his right foot and ankle. The patient was treated in a number of different ways, including two right lumbar paravertebral sympathetic blocks. After each block the patient had resolution of the erythema and hyperesthesia, but the burning pain persisted. The patient was ultimately treated with an injection of 20 mL of 0.5% lidocaine into the caudal epidural space, followed by a continuous lumbar epidural infusion of 0.125% bupivacaine for 72 h with resolution of his pain. The authors suggest that this may show the importance of a pathologic afferent-to-efferent feedback loop in this patient's causalgia. They imply that this loop was somatic as the lumbar paravertebral sympathetic blocks were not successful in relieving all of the patient's symptoms; however, in the article the authors do not document complete sympathetic blockade after lumbar paravertebral sympathetic block. Abolition of the sympathogalvanic response and abolition of sweating (as measured by sweat tests) are the standard tests of complete sympathetic blockade (4–7). Because apparently neither of these tests was used, it is uncertain whether complete or even partial sympathetic blockade was obtained after the lumbar paravertebral sympathetic blocks. Skin temperatures were also not reported. What this case may represent is incomplete sympathetic blockade with partial resolution of symptoms after lumbar paravertebral sympathetic block. It then becomes confusing trying to decide whether the epidural infusion of local anesthetic worked by blocking a pathologic afferent-to-efferent nerve conduction loop, as proposed by the authors, or if it worked by simply blocking sympathetic fibers that were not adequately blocked by the lumbar paravertebral sympathetic blocks.

The authors did not document a sensory level with the epidural infusion. Did the patient obtain pain relief because of sympathetic or somatic blockade? They state the bupivacaine concentration in the infusion relieves somatic pain. However, the patient experienced complete pain relief after the caudal block with 0.5% lidocaine. Did this concentration provide somatic or probably just sympathetic block in this patient?

What the authors may have again demonstrated is that the epidural route is another way to perform sympathetic blockade when technical difficulties prevent obtaining an adequate block via the lumbar paravertebral method. However, it is important to point out the benefits of sympathetic blockade via the lumbar paravertebral route as opposed to the epidural route. First, anatomic separation of sympathetic and somatic pathways with the former technique prevents much of the uncertainty of appropriate diagnosis and treatment. Second, the unilateral sympathetic blockade associated with the lumbar paravertebral method avoids the hypotension commonly seen after the bilateral sympathetic blockade produced with the epidural route and therefore provides for shorter recovery time for outpatients. Neurolytic blockade may be performed with essentially no loss of sensory or motor function in those cases where it is needed (8). Furthermore, in some patients epidural block even with a T-5 sensory level may not completely block the sympathetic fibers to the leg (5). The lower extremity sympathetic block associated with epidural analgesia does not last as long as the sensory block as the former frequently dissipates when the sensory level reaches T-10 (9). In light of this, is the duration of sympathetic blockade with the paravertebral route greater than with the epidural route, and, if so, does this longer duration make the former superior for the treatment of causalgia? Further studies are needed.

In conclusion, complete sympathetic blockade needs to be documented before deciding that a painful condition is not sympathetically mediated. It would be interesting to test the authors' hypothesis in patients who have inadequate pain relief despite complete sympathetic blockade from lumbar paravertebral sympathetic block.

Brian D. Smith, MD
James J. Gibbons, MD
Department of Anesthesiology
St. Louis University
St. Louis, MO 63110

©1991 by the International Anesthesia Research Society

References

1. Lee VC. When sympathectomy fails to relieve causalgic burning pain. Anesth Analg 1990;71:313–4.
2. De Jong RH. Neuropathic pain may not respond to sympathetic blockade. Anesth Analg 1990:71:314.
3. Cicala RS, Jones JW, Westbrook LL. Causalgic pain responding to epidural but not to sympathetic nerve blockade. Anesth Analg 1990;70: 218–9.
4. Benzon HT. Increase in skin temperature, by itself, may not indicate complete sympathetic blockade. Anesth Analg 1988;67:716.
5. Benzon HT, Cheng SC, Avram MJ, Molloy RE. Sign of complete sympathetic blockade: sweat test or sympathogalvanic response? Anesth Analg 1985;64:415–9.
6. Lewis LW. Evaluation of sympathetic activity following chemical or surgical sympathectomy. Anesth Analg 1955;34:334–5.
7. Benzon HT, Avram MJ. Temperature increases after complete sympathetic blockade. Reg Anesth 1986;11:27–30.
8. Cousins MJ, Bridenbaugh PO. Neural blockade in clinical anesthesia and management of pain. 2nd ed. Philadelphia: JB Lippincott, 1988:461–4, 887–9.
9. Kim JM, LaSalle AD, Parmley RT. Sympathetic recovery following lumbar epidural and spinal analgesia. Anesth Analg 1977;56:352–5.

A "Loading Port" for Syringe Infusion Pumps

Key Words: EQUIPMENT, SYRINGE INFUSION PUMPS

To the Editor:

With the increased use of continuous infusions in anesthesia and intensive care, there is more use of syringe infusion pumps. Although the syringe volume is limited and the surgical time is often unknown, there are instances of wasted drugs or cumbersome refilling procedures during anesthesia. We suggest the following "loading port" technique to eliminate these problems.

Before filling the syringe with the drug to be given, a three-way stopcock is placed between the pump syringe and the tubing going to the patient (Figure 1). The tubing is then primed in the usual way with the stopcock opened to the patient. When the volume in the pump syringe runs low, a separate second syringe, the reloading syringe aseptically loaded with the same agent, is attached to the stopcock side port. The plunger of the pump syringe is then disconnected from the pump, and the driving mechanism is retracted. The stopcock is opened to the pump syringe, and the contents of the reloading syringe are injected into the pump syringe (Figure 2). At this point, the driving mechanism is reattached, the stopcock again is reopened to the patient, and the infusion continues.

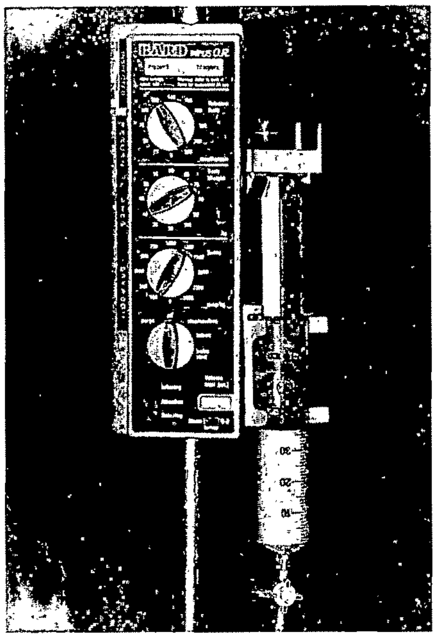


Figure 1. Syringe and pump with three-way stopcock in place.

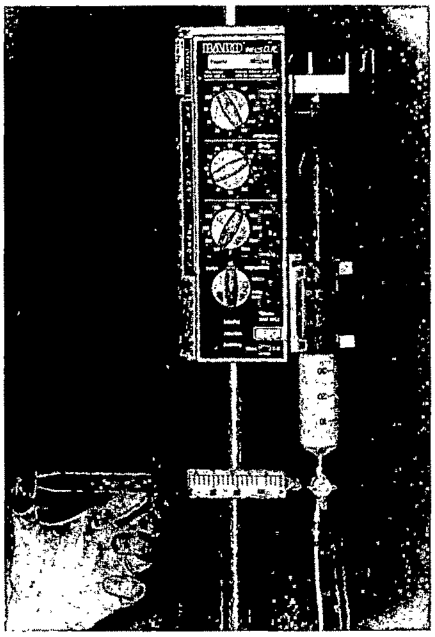


Figure 2. Loading port in use.

We propose this technique for two reasons. First, given the simplicity of this reloading technique, the anesthesiologist is able to load smaller amounts and volumes of drugs more frequently. This allows for more cost-effective use of intravenous agents. With other reloading techniques, the tendency was to fill the entire syringe at the beginning of the case, and if reloading became necessary, to refill the entire syringe again by disconnecting the tubing and taking the syringe out of the pump. As this procedure was time-consuming, the tendency was to err on the conservative side which resulted in wasted drug.

Second, we believe that this technique is associated with greater sterility than are other methods of refilling the pump syringe. The connection between syringe and patient is never broken; all refilling is through the previously attached stopcock. There are no loose tubing ends during the reloading and, therefore, less chance of contamination. There have been recent reports of contaminated intravenous infusions of propofol (Diprivan) when aseptic technique was not observed (1). By using the technique that we propose, contamination of intravenous solution should be minimized.

Given the benefits of sterility, ease of reloading, and less agent wastage, the reloading port is well worth the small additional cost of the stopcock. We have used this port for the Bard InfusO.R. pump (C. R. Bard Inc., North Reading, Mass.) and the Baxter Auto Syringe (Baxter Health Care Corp., Hooksett, N.H.) infusion pumps and believe that it can probably be easily adapted for use in other syringe infusion pumps.

Richard P. O'Flynn, MD
Janet N. Siler, MD
Department of Anesthesiology
Hahnemann University
MS 310
Broad and Vine Streets
Philadelphia, PA 19102

Reference

1. Postsurgical infections associated with an extrinsically contaminated intravenous anesthetic agent—California, Illinois, Maine, and Michigan, 1990. MMWR 1990;June 29:426–7.

Are the Hemodynamic Effects of Dexmedetomidine Influenced by the Background Anesthetic?

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—dexmedetomidine.

To the Editor:

Karlsson et al. recently published data that describe the cerebral blood flow (CBF) and cerebral metabolic rate for oxygen ($CMRo_2$) responses to the administration of dexmedetomidine in dogs (1). Their findings agree with our previously published study in dogs using similar methodology (sagittal sinus venous outflow) and dose of dexmedetomidine (2). In both studies, CBF decreased significantly and $CMRo_2$ was unchanged after the administration of 10 μg/kg of dexmedetomidine given as an infusion over 10 or 15 min. However, the two studies were different in that we used 0.5 MAC isoflurane as the background anesthetic, whereas Karlsson et al. used 1.0 MAC halothane. Our animals all developed a marked hypertensive response to the administration of dexmedetomidine. Likewise, Bloor et al. reported that mean arterial pressure increased significantly in dogs anesthetized with 1.0 MAC isoflurane given 20 μg/kg dexmedetomidine over 2 min (3). In contrast, the animals of Karlsson et al. did not become hypertensive. In agreement with this observation of Karlsson et al. regarding hemodynamic responses to dexmedetomidine administration is an earlier study of Vickery et al. in which no increase in blood pressure was noted in halothane-anesthetized dogs given the same dose of dexmedetomidine (4).

We wonder if these differing hemodynamic responses might be a function of the anesthetic state (halothane vs isoflurane). If the hemodynamic responses to the administration of dexmedetomidine are dependent on the particular volatile anesthetic background state, this would seem to be a novel drug interaction worthy of further careful investigation.

The fact that our isoflurane-anesthetized dogs all became quite hypertensive and yet still demonstrated significant decreases in cerebral blood flow attests to the potent global cerebral vasoconstrictor properties of dexmedetomidine. However, whether or not this property would be of use in neurosurgical patients will depend on the ability of dexmedetomidine to alter local cerebral blood flow to provide favorable flow redistribution to ischemic or penumbral areas rather than simply to decrease global cerebral blood flow per se. This would also seem to be a potential avenue for further study.

Mark S. Scheller, MD
Mark H. Zornow, MD
Department of Anesthesiology
UCSD School of Medicine
9500 Gilman Drive
La Jolla, CA 92093-0629

References

1. Karlsson BR, Forsman M, Roald OK, Heier MS, Steen P. Effect of dexmedetomidine, a selective and potent α_2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 1990;71:125–9.
2. Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an α_2-adrenergic agonist, decreases cerebral blood flow in the isoflurane anesthetized dog. Anesth Analg 1990;70:624–30.
3. Bloor BC, Alper G, Frankland M, Flacke JW. Nifedipine attenuates the acute hemodynamic changes that occur with intravenous dexmedetomidine in dogs (abstract). Anesth Analg 1989;68:S32.
4. Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α_2-adrenergic agonist in halothane-anesthetized dogs. Anesth Analg 1988;67:611–5.

In Response:

As pointed out by Drs. Scheller and Zornow, our findings (1) correspond well with the results from their study (2), which were published 2 mo before our own.

Drs. Zornow and Scheller raise the question whether the hemodynamic effects of dexmedetomidine are influenced by the background anesthetic. They compare the results from four studies during isoflurane or halothane anesthesia. We have gathered the available data on the effect of α_2-adrenergic agonists on systemic hemodynamic variables during inhalation anesthesia in Table 1 (1–7). In our studies a transient increase in mean arterial pressure was seen during the drug infusion, but the blood pressure returned to preinfusion levels before the next set of measurements were obtained. From the tabulated data, it seems most likely that the effect of dexmedetomidine on mean arterial pressure during inhalation anesthesia is dependent on the dose of the anesthetic and the α_2-agonist and not on the anesthetic agent per se. This view is also supported by data from Maze et al. (6) and from our own group (data not published) on the effects of azepexole, another potent α_2-agonist, on cerebral blood flow and $CMRo_2$ during 1 MAC isoflurane anesthesia. Azepexole (1 mg/kg) (equipotent reduction in MAC for isoflurane or halothane to 10

Table 1. Available Data on the Effect of α_2-Adrenergic Agonists on Hemodynamic Variables During Inhalation Anesthesia

Authors	Anesthetic	α_2-Agonist	Dose	HR	CO	MAP	SVR
Bloor et al.[a]	Iso 1 MAC	Dexmedetomidine	20 μg/kg	↓	↓	↑	↑
Zornow et al.	Iso 0.5 MAC	Dexmedetomidine	10 μg/kg	↓	↓	↑	
Bloor et al.[a]	Iso 1 MAC	MPV-1440	20μg/kg	↓	↓	↑	↑
Vickery et al.	Hal 1 MAC	Dexmedetomidine	1–10 μg/kg	↓	↓	No change	(↑)NS
Karlsson et al.	Hal 1 MAC	Dexmedetomidine	10 μg/kg	↓		No change	
Maze et al.	Iso 1 MAC	Azepexole	0.1–1 mg/kg	↓	↓	No change	(↑)NS
Raybould et al.[a]	Iso 1 MAC	BHT-920	0.1–0.3 mg/kg	↓	↓	No change	↑
Karlsson et al.[b]	Iso 1 MAC	Azepexole	1 mg/kg	(↓)NS		No change	

HR, heart rate; CO, cardiac output; MAP, mean arterial pressure; SVR, systemic vascular resistance; Iso, isoflurane; Hal, halothane; NS, nonsignificant.
[a] Abstract.
[b] Data not published.

μg/kg dexmedetomidine) caused a reduction in the cerebral blood flow, whereas neither $CMRo_2$ nor mean arterial pressure was affected by drug administration.

Dexmedetomidine, as well as azepexole, has been shown to have a centrally mediated hypotensive effect (8,9). In conscious dogs (10), or when intravenous or intraperitoneal anesthetics were given to cats, dogs, or rats (8,9), the hypotensive effect of the drug dominated at the dose levels used. Thus it is possible that the inhalation anesthetics interact with the α_2-agonists in a way different from other classes of anesthetics because no hypotensive effect of these drugs could be demonstrated during halothane or isoflurane anesthesia.

Bente R. Karlsson, MD
Institute for Experimental Medical Research

Petter A. Steen, PhD
Department of Anesthesiology
Ullevål Hospital
0407 Oslo 4, Norway

References

1. Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent α_2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg 1990;71:125–9.
2. Zornow MH, Fleischer JD, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, an α_2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg 1990;70:624–30.
3. Bloor BC, Alper G, Frankland M, Flacke JW. Nifedipine attenuates the acute hemodynamic changes that occur with intravenous dexmedetomidine in dogs (abstract). Anesth Analg 1989;68:S32.
4. Bloor BC, Raybould D, Shurtliff M, Gellmann J, Stead SW. MPV-1440, an alpha$_2$ adrenergic agonist with potent anesthetic qualities. Anesthesiology 1988;69:A614.
5. Vickery RG, Sheridan BC, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α_2-adrenergic agonist, in halothane-anesthetized dogs. Anesth Analg 1988;67:611–5.
6. Maze M, Vickery RG, Merlone SC, Gaba DM. Anesthetic and hemodynamic effects of the alpha$_2$-adrenergic agonist, azepexole, in isoflurane-anesthetized dogs. Anesthesiology 1988;68:689–94.
7. Raybould D, Bloor BC, McIntee DF, Flacke JW, Flacke WE. Reduction of anesthetic requirement and cardiovascular effects of BHT-920, a selective alpha$_2$ adrenergic agonist. Anesthesiology 1988;69:A600.
8. Kobinger W, Pichler L. Pharmacological characterization of B-HT 933 (2-amino-6-ethyl-4,5,7,8-tetrahydro-6H-oxazolo-(5,4-*d*)-azepin-dihydrochloride) as a hypotensive agent of the "clonidine-type." Naunyn-Schmiedebergs Arch Pharmacol 1977;300:39–46.
9. Savola JM, Ruskoaho H, Puurunen J, Salonen JS, Kärki NT. Evidence for medetomidine as a selective and potent agonist at α_2-adrenoceptors. J Auton Pharmacol 1986;5:275–84.
10. Schmeling WT, Kampine JP, Warltier DC. Hemodynamic actions of the stereoisomers of the α_2-adrenergic agonist medetomidine in concious dogs (abstract). Anesth Analg 1990;70:S351.

Harold Griffith and John Snow

Key Words: HISTORY, HAROLD GRIFFITH, SIR ROBERT MACINTOSH, JOHN SNOW.

To the Editor:

Drs. Maltby and Bamforth's interesting story (1) of Ralph Waters, Sir Robert Macintosh, and John Snow's book *On Chloroform and Other Anaesthetics* deserves a foreword. The seventy-fifth anniversary of the death of John Snow was honored at the Twelfth Annual Congress of Anesthetists in 1933 at Chicago during the "Century of Progress" World Fair. The Congress was sponsored by the Associated Anesthetists of the United States and Canada, the International Anesthesia Research Society, the Eastern Society of Anesthetists, the Mid-Western Association of Anesthetists, the Southern Association of Anesthetists, and the Clinical Congress of Surgeons. Harold Griffith was president and entitled his presidential address "John Snow, Pioneer Specialist in Anesthesia." He quoted at length from *On Chloroform* and was evidently quite familiar with it. There is no copy, however, amongst his memorabilia at the Queen Elizabeth Hospital in Montreal, where he spent his working life. Sir William Osler's own copy of the 1858 edition is in the Osler Library of the History of Medicine at McGill University, where it was deposited with the bequest that established that library after his death in 1919. As a McGill graduate and Montreal physician, Harold Griffith would have had access to it.

Sir Robert Macintosh would have met Harold Griffith at a "Special Meeting" of the American Society of Anesthetists with the inaugural meeting of the Section of Anesthesia of the Connecticut State Medical Society, of which Brian Sword was chairman, held at Bridgeport on May 20, 1937. Macintosh addressed the meeting as a guest, and Harold

Griffith read a paper entitled "The Recent Revolution in Anesthesia."

Griffith was a particular friend of Waters, as a fellow member of the Anesthetist's Travel Club since 1930. There seems little doubt that his presidential address contributed to the revival of interest in John Snow, at a time when Waters did not have a copy of *On Chloroform and Other Anaesthetics* and Macintosh had not read it; he later admitted "Snow was virtually unknown to British anaesthetists of my generation."

I am indebted to the Wood Library-Museum for allowing me to look at the Minutes of the ASA Meeting of 1937.

Richard I. Bodman, MB, FRCP(C)
1 Prince Street, Suite 409
Dartmouth, Nova Scotia
Canada B2Y 4L3

Reference

1. Maltby JR, Bamforth BJ. The Wood Library-Museum's 1858 edition of John Snow's *Chloroform and Other Anaesthetics*. Anesth Analg 1990;71:288–94.

Severe Hypocapnia During Cardiopulmonary Bypass

Key Words: CARBON DIOXIDE, HYPOCAPNIA—during cardiopulmonary bypass. ANESTHESIA, CARDIOVASCULAR—cardiopulmonary bypass. EQUIPMENT, FLOW METERS—malfunction.

To the Editor:

Hypocapnia during cardiopulmonary bypass (CPB) may be associated with decreases in cerebral blood flow (1), possible neurologic deficits (2), leftward shift of the oxyhemoglobin curve (3), and decreases in coronary blood flow (4). We were involved recently in a case of severe hypocapnia due to an unrecognized problem with the air-oxygen mixer flow meter used during CPB.

A 64-yr-old man, ASA physical status IIIE with unstable angina and severe three-vessel coronary artery disease, was admitted for urgent coronary artery bypass operation. A high-dose sufentanil technique was used, and the case proceeded uneventfully during the pre-CPB and early CPB period. On CPB, moderate hypocapnia was present during the initial cooling period (Table 1). (All arterial blood gas tensions are uncorrected using alpha-stat management.) During rewarming, despite attempts to decrease oxygen flows to the membrane oxygenator (Bentley BOS CM 50), the arterial partial pressure of carbon dioxide ($Pa{CO_2}$) continued to decrease. Arterial blood gas tensions were measured using an Instrumentation Laboratories IL 1312 machine and were confirmed by a second independent ABG analysis (radiometer ABL-3). Oxygen flow was apparently decreased from 3.5 L/min to a markedly low 500 mL/min without normalization of $Pa{CO_2}$ (Table 1). During this period, there were no dysrhythmias or evidence of myocardial ischemia determined by computerized electrocardiographic ST segment analysis. Cerebral blood flow determination and electroencephalographic analysis were not performed.

At the time, no cause could be found for the hypocapnia. The decision was made to attempt discontinuation of CPB despite the abnormality of the acid-base status. After discontinuation of CPB, the patient's condition remained stable and he was taken to the intensive care unit. His postoperative course was uneventful. Although formal neuropsychiatric testing was not performed, no evidence of central nervous system dysfunction was evident at the time of discharge from the hospital on the 10th postoperative day.

The air-oxygen mixer (model No. 14810, Sechrist Industries, Inc., Anaheim, Calif.) consists of two flow meters. The left flow meter regulates flow from 0 to 1000 mL/min. The right flow meter regulates flow from 0 to 10 L/min (Figure 1). These flow meters are in *parallel* not in series. In adults, the 0–10-L/min flow meter is used exclusively at our institution, and the 0–1000-mL/min flow meter should be in the "OFF" position (Figure 1). After the case described above was finished, the flow meters of the air-oxygen mixer were evaluated. On inspection, the 0–1000-mL/min flow meter was "ON" and the flotation ball was above the 1000-mL/min mark (Figure 2). Testing flows (with a Wright spirometer) through the 0–1000-mL/min flow meter revealed a marked discrepancy between indicated and actual flows. In Figure 1, the left flow meter is off, the right flow meter indicates 2 L/min, and total measured flow equaled 2 L/min. The 0–1000-mL/min flow meter was then turned on, the knob controlling the flow being turned counterclockwise three revolutions past 1000-mL/min flow to simulate the situation during the case. The flotation ball of this flow meter is seen above the 1000-mL mark in Figure 2. In this configuration, measured flow was 42 L/min.

We assume that the flow meter was set in this position accidentally before CPB. Our belief that this flow meter is usually off during adult cases and the fact that the flotation ball was difficult to see, led to the assumption that this flow meter was off during CPB. It appears that approximately 50 psi of pressure and more than 40 L/min of flow were delivered from the air-oxygen mixer to the oxygenator. We contacted the Sechrist Corporation, and they were unaware of this potential complication.

The $Pa{CO_2}$ during CPB is regulated by flow (sweep rate) to the oxygenator (5). Increasing the sweep rate decreases $Pa{CO_2}$, and decreasing the sweep rate increases $Pa{CO_2}$. Moderate hypocapnia induced by lung ventilation during CPB is usually moderate (6). The lungs were not ventilated at the time the hypocapnia developed in the patient.

Markedly increased flows to the oxygenator caused severe hypocapnia and respiratory alkalosis in this patient. It was fortunate that this did not cause any identifiable long-term sequelae, but the potential damage of severe hypocapnia that we observed in this instance should be known to anesthesiologists. It can be prevented in three ways:

1. Checking all flow meters to determine they are in the "OFF" position before starting CPB.

Table 1. Arterial Blood Gas Tensions in the Perioperative Period

Time	Events	"Apparent" sweep rates[a] (L/min)	pH	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)	HCO_3 (mEq/L)	Blood temp (°C)
1345	Pre-CPB	—	7.41	36	418	23.0	36.2
1455	Cannulation	4.5	7.45	32	366	22.3	33.4
1500	On CPB	3.0	7.66	19	346	21.4	28.8
1522	Cooling	3.5	7.64	20	166	21.4	26.6
1555	Graft anast	3.0	7.70	13	399	—	28.2
1610	Warming	2.0	7.85	11	402	18.9	36.0
1630	Before weaning from CPB	0.5	7.80	12	479	18.2	35.8
1720	Off CPB	—	7.35	39	277	21.3	36.3
1845	End of operation	—	7.36	33	346	17.9	36.7

$Paco_2$, partial pressure of carbon dioxide, arterial; Pao_2, partial pressure of oxygen, arterial; Anast, anastomosis; CPB, cardiopulmonary bypass.
[a] Flow rates set on air-oxygen mixer going to oxygenator in liters per minute (see text).

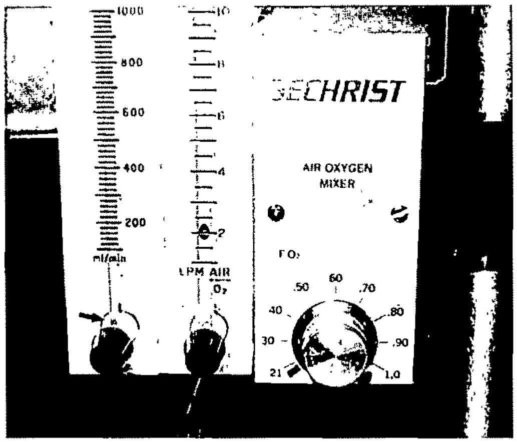


Figure 1. Flow meters on air-oxygen mixer of CPB machine. *Arrow* points to flotation ball of 0–1000-mL/min flow meter when in "OFF" position.

2. Increased understanding of all CPB equipment. Our familiarity with anesthesia machines led us to believe that the flow meters used during CPB are in series when in fact they are in parallel. Our assumption that the 0–1000-mL/min flow meter output would be *included* in the reading of the 0–10-L/min flow meter (in series configuration) was incorrect.
3. Checking the flow from the air-oxygen mixer. Brief disconnection of the tubing from the oxygenator and "listening" to the flow would probably have led to prompt discovery of this problem.

We hope this letter will alert anesthesiologists to this potential complication and stimulate increased knowledge of CPB equipment.

Mark E. Romanoff, MD
Department of Anesthesiology/SGHSA
Wilford Hall USAF Medical Center
Lackland AFB, TX 78236-5300

Philip W. Kocoloski, DO
Department of Anesthesiology/SGHSA
USAF Medical Center
Wright-Patterson AFB, OH 45433

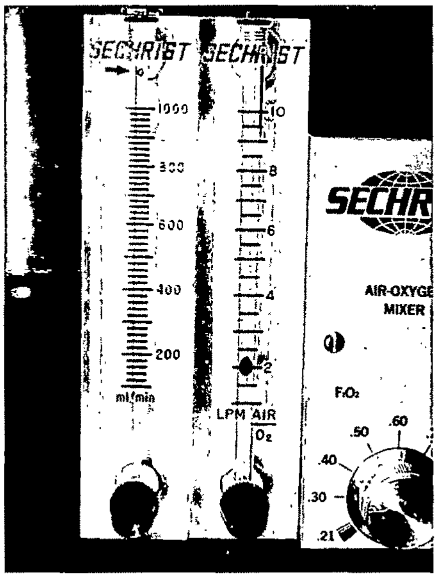


Figure 2. *Arrow* points to flotation ball of 0–1000-mL/min flow meter when control knob was turned counterclockwise three revolutions past 1000-mL/min flow (see text).

References

1. Johnsson P, Messeter K, Ryding E, et al. Cerebral vasoreactivity to carbon dioxide during cardiopulmonary perfusion at normothermia and hypothermia. Ann Thorac Surg 1989;48:769–75.
2. Nevin M, Adams S, Colchester ACF, Pepper JR. Evidence for involvement of hypocapnia and hypoperfusion in aetiology of neurological deficit after cardiopulmonary bypass. Lancet 1987;ii:1493–5.
3. Ranney HM, Sharma VS. Hematology. In: Williams WJ, ed. Structure and function of hemoglobin. New York: McGraw Hill, 1990:377–88.
4. Coetzee A, Holland D, Foex P, et al. The effect of hypocapnia on coronary blood flow and myocardial function in the dog. Anesth Analg 1984;63: 991–7.
5. Reed CC, Stafford TB. Cardiopulmonary bypass. Houston: Texas Medical Press, 1985:427–49.
6. Moore RA, Gallagher JD, Kingsley BP, Lemole G, Kerns D, Clark DL. The effect of ventilation on systemic blood gases in the presence of left ventricular ejection during cardiopulmonary bypass. J Thorac Cardiovasc Surg 1985;90:287–90.

β-Adrenergic Receptor Function in Surgical Patients

Key Words: SYMPATHETIC NERVOUS SYSTEM, β-ADRENERGIC RECEPTORS. RECEPTORS, β-ADRENERGIC.

To the Editor:

I read with interest the article by Marty et al. (1) that reported increased β-adrenergic receptor (β-AR) density of the lymphocyte membrane and slightly decreased β-AR isoproterenol affinity in surgical patients demonstrating adrenergic activation. Dr. Marty clearly demonstrates that adrenergic activation occurs in a subpopulation of surgical patients and that these changes correlate nicely with the receptor changes detailed above. Adrenergic receptor desensitization is an important laboratory and clinical phenomenon that is subtle and occasionally difficult to interpret. Therefore, I would like to make a few comments that might help the reader interpret Dr. Marty's data in this difficult area.

First of all, the study of adrenergic receptor function during anesthesia and operation is important yet fraught with difficulty. For example, in studies using circulating lymphocytes as a monitor of adrenergic receptor function, strict controls for lymphocyte subpopulations are required as varying lymphocyte populations have different β-AR density (2). In studies in which elevated catecholamines are induced by catecholamine infusions (2,3) or by exercise (4), artifactual increases in apparent β-AR density occur due to recruitment of lymphocytes located in tissues such as the spleen that have different (higher overall) β-AR density (2). Hence, strict controls for lymphocyte subpopulations need to be observed in studies using lymphocyte β-AR function before conclusions can be drawn. Although the most definitive manuscript in this area (2) was published after Dr. Marty's paper was submitted to *Anesthesia and Analgesia,* it is important to point out that the increased β-AR number found in Dr. Marty's study is probably due to recruitment of new lymphocyte subpopulations in these patients simply because of the presence of elevated catecholamines and therefore unrelated to desensitization. Second, with regard to the small changes in β-AR isoproterenol affinity in surgical patients demonstrating adrenergic activation in this study, the data regarding K_L (dissociation constant for isoproterenol, specifically low-affinity binding sites) or IC_{50} (concentration of isoproterenol required to displace 50% of specific binding) may well represent lymphocyte β-AR desensitization in these patients. However, it is difficult to be sure such small changes are relevant until a measure of β-AR function, such as adenylyl cyclase activity, is assessed. Dr. Marty and his colleagues suggest this themselves in their discussion.

Again, I congratulate Dr. Marty and his coauthors for attempting to elucidate the response of the adrenergic nervous system in the surgical patient. Further studies using functional data (such as adenylyl cyclase activity) may elucidate potential mechanisms of β-AR desensitization during anesthesia and operation.

Debra A. Schwinn, MD
Department of Anesthesiology
Duke University Medical Center
Durham, NC 27710

References

1. Marty J, Nimier M, Rocchiccioli C, et al. β-Adrenergic receptor function is acutely altered in surgical patients. Anesth Analg 1990;71:1–8.
2. Van Tits LJH, Michel MC, Grosse-Wilde H, et al. Catecholamines increase lymphocyte β_2-adrenergic receptors via a β_2-adrenergic, spleen-dependent process. Am J Physiol 1990;258:E191–202.
3. Tohmeh JF, Cryer PE. Biphasic adrenergic modulation of β-adrenergic receptors in man. J Clin Invest 1980;65:836–40.
4. Brodde O-E, Daul AE, Wang XL, Michel MC, Galal O. Dynamic exercise-induced increase in lymphocyte beta-2-adrenoceptors: abnormality in essential hypertension and its correction by antihypertensives. Clin Pharmacol Ther 1987;41:371–9.

In Response:

We appreciate Dr. Schwinn's comments and agree that an increase in β-adrenergic receptor (B-AR) density may be due to recruitment of new lymphocyte subpopulations related to elevated catecholamines (1). However, this explanation was documented only in 1990, that is after the acceptance of our manuscript. We did not relate this change in B-AR density to desensitization but rather to an increase in plasma concentration of cortisol as it has been documented previously (2). In fact, the most important finding of our study is the decrease of B-AR isoproterenol affinity, which may well represent desensitization. As mentioned, we did not assess B-AR function by a measure of adenylyl cyclase activity. Nevertheless, we observed in some patients an alteration of the usually observed hemodynamic responses to adrenergic activation at the time of recovery that was highly suggestive of B-AR desensitization. Obviously, further studies are needed to delineate exactly the mechanisms of these alterations.

Jean Marty, MD
Martin Nimier, MD
Hôpital Bichat
46 rue Henri Huchard
75018 Paris, France

References

1. Van Tits LJH, Michel MC, Grosse-Wilde H, et al. Catecholamines increase lymphocyte β_2-adrenergic receptors via a β_2-adrenergic, spleen-dependent process. Am J Physiol 1990;258:E191–202.
2. Hui KKP, Conoly ME, Tashkin DP. Reversal of human lymphocyte beta-adrenoceptor desensitization by glucocorticoids. Clin Pharmacol Ther 1982;32:566–71.

A History of Nurse Anesthesia?

Key Words: HISTORY, NURSE ANESTHESIA.

To the Editor:

I read with interest Dr. Selma Harrison Calmes's review of Marianne Bankert's book, *Watchful Care: A History of Amer-*

ica's Nurse Anesthetists. It is most interesting to note that several important political issues were not discussed in the volume. First and foremost, with the hiring of John Silas Lundy, MD, as the chief of anesthesia, the Mayo Clinic switched from a nurse-dominated to a physician-dominated department. Why did the Mayo brothers feel, in the mid-1920s, that this was necessary? How did this change affect the nurse anesthetists? Did "the mother of anesthesia," as Marianne Bankert refers to Alice Magaw, go quietly into the night when Lundy arrived?

Second, although Bankert chronicles the rise of the American Association of Nurse Anesthetists (AANA) in the 1930s, she never mentions the contemporary rise of the physician anesthetists. Both the International Anesthesia Research Society and the American Society of Anesthetists were very active in promoting the "science and art of anesthesia," which was capped by an exhibit at the 1939 New York World's Fair. (The American Society of Anesthetists, a physician organization, became the American Society of Anesthesiologists in 1945.)

Last, as Dr. Calmes so accurately pointed out, Bankert's book includes little contemporary history. As the number of schools of nurse anesthesia declines, which has shrunk the AANA's political base, the organization has grown in power. This seeming contradiction in terms needs to be further explored as does the relationship between nurse anesthetists and anesthesiologists. There is much in that association beyond the numerous court battles of the 1920s, 1930s, and 1940s that Bankert so well documents, and perhaps it is time for a truce on all sides.

Douglas R. Bacon, MD
Department of Anesthesiology and Critical Care Medicine
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263

Reference

1. Calmes SH. Watchful care: a history of America's nurse anesthetists (book review). Anesth Analg 1990;71:573–4.

Intraspinal Opiates in Patients Receiving Podophyllum

Key Words: TOXICITY, PODOPHYLLUM. ANESTHETIC TECHNIQUES, EPIDURAL—morphine.

To the Editor:

The paper on delayed recognition of podophyllum toxicity in a patient receiving epidural morphine by Conrad et al. (1) is an interesting report of a phenomenon that is not often seen. The statement, "analgesic techniques such as epidural morphine, which may mimic the signs and symptoms of podophyllum toxicity and delay diagnosis, should therefore be avoided," is an unfortunate extraction of an unjustified conclusion from an interesting observation. The problem in this case was purely and simply a frank overdose of podophyllum. The fact that this patient received epidural morphine is a "red herring." There is absolutely nothing about this clinical course, except for nausea, that could in any way have been attributed to epidural morphine. In fact, epidural morphine side effects *do not* mimic the signs and symptoms of podophyllum toxicity. The age-old dictum that appropriate analgesia may mask pathology is in many cases simply an excuse to justify lack of appropriate clinical observation.

I suggest that a more appropriate conclusion to this article would have been that broader based training of the gynecologic house staff in recognition of the signs of podophyllum toxicity and more intensive education of the nursing and house staff in the signs of side effects of intraspinal opioids are needed (2).

Podophyllum application to condylomata acuminata is painful. Pain after surgical procedures should be appropriately treated by appropriate means. A suggestion for "small doses of analgesics" (1) is a call for inappropriate management of postsurgical pain.

W. Thomas Edwards, PhD, MD
Pain Relief Service
Department of Anesthesiology, ZA-14
Harborview Medical Center
325 Ninth Avenue
Seattle, WA 98104

References

1. Conrad PF, Hanna N, Rosenblum M, Gross JB. Delayed recognition of podophyllum toxicity in a patient receiving epidural morphine. Anesth Analg 1990;71:191–3.
2. Ready LB, Edwards WT. Postoperative care following epidural or intrathecal opioids II. Anesthesiology 1990:72:213.

Propofol Does Not Trigger Malignant Hyperthermia

Key Words: HYPERTHERMIA, MALIGNANT—propofol. ANESTHETICS, INTRAVENOUS—propofol.

To the Editor:

The use of propofol in patients known to have or be at risk for malignant hyperthermia (MH) has not been reported. A recent study showed propofol did not trigger MH in genetically susceptible swine and suggested that propofol is "almost certainly" safe to use in patients at risk for MH (1). The following case confirms this conclusion.

A 15-yr-old, 64-kg boy scheduled for open reduction of a nasal fracture had a documented MH episode 4 yr before admission while undergoing general anesthesia for antral windows. It was elected to attempt surgery using an ester local anesthetic and sedation, with an anesthesia machine free of potentially MH-triggering inhalation anesthetics and with an MH cart in the room. Despite incremental doses of midazolam, alfenta, and propofol, the patient was unable to tolerate surgical manipulation. He was then preoxygenated and anesthesia was induced with propofol followed by atracurium for tracheal intubation. Anesthesia was then maintained with nitrous oxide in oxygen and bolus doses of propofol. His intraoperative and postoperative course was uneventful. He was observed for 24 h and discharged without sequelae.

Dogma has it that we use a balanced nitrous oxide/narcotic anesthetic for patients at risk for MH. One could avoid the delayed emergence often associated with this technique for short surgical procedures by using a drug such as propofol. This case confirms the suggestion based on animal experiments (1) that propofol is safe to use in MH-susceptible patients and offers a valuable alternative in the anesthetic management of these patients.

Jonathan S. Gallen, MD
Department of Anesthesia
Clayton General Hospital
Riverdale, GA 30274

Reference

1. Raff M, Harrison GG. The screening of propofol in MHS swine. Anesth Analg 1989;68:750–1.

Oral Pulse Oximetry in Small Children

Key Words: ANESTHESIA, PEDIATRIC. MEASUREMENT TECHNIQUES, OXIMETRY—pediatric.

To the Editor:

I read with interest the reports by Jobes and Nicolson (1), Gunter (2), and Sosis (3) concerning the utilization of the oral cavity as a possible place for positioning a pulse oximeter probe. I would like to comment on my experience utilizing this approach.

In 1987, while working in a cardiovascular surgical unit in the United Kingdom, I realized that it was difficult to obtain a stable signal with pulse oximetry in small children, especially when they had surgery with extracorporeal circulation and systemic hypothermia. Under those conditions, most pulse oximeters tended to give false readings, probably because of insufficient peripheral perfusion attributable to hypothermia and vasoconstriction. As we did not have access at that time to reliable probes for children, we attempted to use the normal Ohmeda Pulse Oximeter adult ear probe (model 8122-003, Biox 3700, Boulder, Colo.), inserting one of the jaws into the mouth, against the inner surface of the cheek, while the other jaw was apposed to the external surface (Figure 1). This simple procedure allowed us to obtain reliable measurements of the child's blood oxygenation even at moderate degrees of hypothermia, presumably due to the fact that the tissues in this area are relatively thin and well vascularized. Blood flow in this area did not seem to be altered as much as the flow in the ear, finger, or toe in children undergoing cardiac surgery with hypothermia. The probe is easy to place, and the pressure exercised by it seemed to be small as no pressure marks were visible after operations. We found this technique to be extremely useful in small children, including patients under 3 kg body weight with complex congenital heart defects. This is a group of children in whom pulse oximetry may be especially useful.

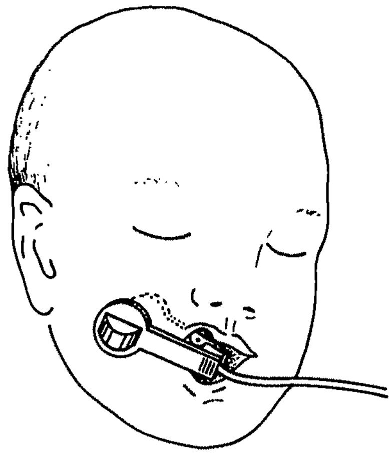


Figure 1. Positioning of adult Ohmeda pulse oximeter in an infant with one of the jaws of the probe on the buccal surface and the other on the cutaneous surface of the cheek.

Gunter (2) suggested that the sensor should be stiffened by a piece of metal, before being placed in the mouth, to secure it in place. In children, I found this to be unnecessary, as the unmodified probe stayed securely in place throughout the operation. This extremely simple technique should be considered when pediatric probes are not available.

Guillermo E. Lema, MD
Department of Anesthesiology
Catholic University of Chile
P.O. Box 114-D
Santiago de Chile, Chile

References

1. Jobes DR, Nicolson SC. Monitoring of arterial hemoglobin oxygen saturation using a tongue sensor. Anesth Analg 1988;67:186–8.
2. Gunter JB. A buccal sensor for measuring arterial oxygen saturation. Anesth Analg 1989;69:417–8.
3. Sosis MB. Use of an Ohmeda ear oximetry probe for "buccal" oximetry. Can J Anaesth 1990;37:489–90.

Why 70 Watts to Evaluate Metal Tapes for CO_2 Laser Surgery?

Key Words: EQUIPMENT, LASERS—flammability.

To the Editor:

Are the conclusions of the study by Sosis (1), evaluating five metallic tapes for protecting endotracheal tubes during carbon dioxide (CO_2) laser surgery, clinically relevant? Surgeons usually prefer tracheal tubes much smaller than 8.0-mm inner diameter, and 70-W power continuous mode seems excessive and inappropriate. Strong et al. (2) described 15 W with a time exposure of ⅕ s for precise microsurgery and 15–25 W continuously for gross dissection, and others believed 20 W adequate for laryngeal surgery (3). Lately, some find 10 W, and less, satisfactory (4), and the trend appears to be toward smaller spot size and lower power settings (5). Patel and Hicks (6) reported that aluminum tape (Radio Shack No. 44-1155) wrapping of red rubber or plastic tubes delayed ignition by the laser at continuous 15 W for about 60 s and at continuous 30 W for around 25 s. Unfortunately, they did not detail the microscope-laser arrangement used, or the gaseous environment for this particular part of their experiments. However, Ossoff (7), utilizing 6.0-mm inner diameter tubes, has recently stated that reflective aluminum tapes 3M No. 425 and Radio Shack No. 44-1155 protected polyvinyl chloride tubes from igniting in 100% oxygen when exposed to 180 s of continuous mode laser energy at 10, 15, or 20 W. Now the surgeon has total visual, positional, and firing control of the laser beam and, even accidentally, should he be likely to make contact with a wrapped tube for a small fraction of these durations—let alone at 70 W? As Sosis (1) points out, reports often fail to specify the type of tape used. They also may omit the dimensions of the tape employed (6,7), the extent of overlap of each turn of the wrapping (1,6,7,8), or, in experiments, whether the laser was aimed at a single or a double (i.e., overlap) layer of the aluminum tape (6,7). It would be helpful if all of these were always defined. Sosis (1) used 0.6-cm (0.25-in) self-adhesive foil tape but 0.4–1.0-cm (8) and 1.2-cm (0.5-in) (9) tapes have also been recommended. We, unfortunately, have only 1.8- and 2.5-cm-wide tapes, which we cut to appropriate sizes. Overlap suggestions have included "just enough that the laser does not get under the edge but not too much or the tape will acquire creases" (9), at least ⅓–½ tape width (10), ½ width (11), and at least ½ width (12) of the previous turn.

Finally, descriptions of tape wrapping also frequently lack detail. I found it an informative exercise to wrap various sizes of endotracheal tubes with tapes of different widths and degrees of overlap; in this way one gets some idea of the way in which these latter might relate to the potential for complications. For example, the spiral of the tape on the tube is more horizontal for greater overlap, more vertical for lesser degrees of overlap, and for any degree of overlap a narrower tape can be applied in a more horizontal, or less vertical, spiral on the tube than can a wider tape. Also, an overlap of half the tape width ensures an overall protective double thickness of tape on the tube as well as enabling the tape edge to abut against the ridge from the previous turn for a possibly smoother surface. Lesser degrees of overlap give alternating bands of single and double tape layers and thus a lesser overall protection to the tube. Flexibility is less with greater overlap, particularly for wider tapes, and tube flexion can lead to kinking, or to crinkling, creasing, edge prominence, or partial tape separation. Gaps exposing the tube to the laser are then possible as, also, with small overlaps. Narrow tapes have more turns and edges and smaller overlaps. Differing circumstances could require compromises.

R. Williamson, Bsc, MB, ChB, DA
Department of Anaesthetics
University of Natal, Faculty of Medicine
P.O. Box 17639
Congella 4013
South Africa

References

1. Sosis MB. Evaluation of five metallic tapes for protection of endotracheal tubes during CO_2 laser surgery. Anesth Analg 1989;68:392–3.
2. Strong MS, Jako GJ, Polanyi T, Wallace RA. Laser surgery in the aerodigestive tract. Am J Surg 1973;126:529–33.
3. Vourc'h G, Tannieres ML, Freche G. Anaesthesia for microsurgery of the larynx using a carbon dioxide laser. Anaesthesia 1979;34:53–7.
4. Pashayan AG, Gravenstein JS, Cassisi NJ, McLaughlin G. The helium protocol for laryngotracheal operations with CO_2 laser: a retrospective review of 523 cases. Anesthesiology 1988;88:801–4.
5. Shapshay SM, Wallace RA, Kveton JF, Hybels RL, Setzer SE. New microspot micromanipulator for CO_2 laser application in otolaryngology—head and neck surgery. Otolaryngol Head Neck Surg 1988;98:179–81.
6. Patel KF, Hicks JN. Prevention of fire hazards associated with use of carbon dioxide lasers. Anesth Analg 1981;60:885–8.
7. Ossoff RH. Laser safety in otolaryngology—head and neck surgery: anesthetic and educational considerations for laryngeal surgery. Laryngoscope 1989;99(Suppl 48):1–26.
8. Hermens JM, Bennett MJ, Hirshman CA. Anesthesia for laser surgery. Anesth Analg 1983;62:218–29.
9. Wainwright AC. Anaesthesia for CO_2 laser surgery. In: Carruth JAS, Simpson GT, eds. Lasers in otolaryngology. London: Chapman & Hall, 1988:35–45.
10. Healy GB. Complications of laser surgery. Otolaryngol Clin North Am 1983;16:815–20.
11. Simpson GT. The laser in laryngeal disease. In: Carruth JAS, Simpson GT, eds. Lasers in otolaryngology. London: Chapman & Hall, 1988:47–86.
12. Davis RK, Simpson GT. Safety with CO_2 laser. Otolaryngol Clin North Am 1983;16:801–13.

In Response:

I wish to thank Dr. Williamson for his interest in my investigations of metallic foil wrapping for the protection of endotracheal tubes during CO_2 laser surgery (1).

A CO_2 laser power output of 70 W in the continuous mode of operation was chosen in this study to provide the most stringent test of foil wrapping endotracheal tubes that we could devise. Any foil wrapping satisfactorily protecting an endotracheal tube under these conditions should offer a comfortable margin of safety when used in clinical practice, as long as it is utilized properly. This is important because the laser might be inadvertently set to a higher power than realized. Also, some surgeons frequently use the continuous mode even though the pulsed (shuttered) mode is considered to be safer.

As Dr. Williamson correctly notes, newer lasers often incorporate a smaller beam diameter. The result is that at a given power output, the power density (power/area) of the laser will be increased. This will pose a more severe test of a foil-wrapped endotracheal tube than would a larger beam diameter.

Blowtorch ignition of polyvinylchloride endotracheal tubes wrapped with Radio Shack No. 44-1155 occurred in our tests. Although such combustion might not occur during a less stringent evaluation, I see no reason to use this tape clinically when safer ones are available.

The size 8.0-mm inner diameter endotracheal tubes evaluated in my study may often not be appropriate for laser airway surgery; however, I believe the results of this study will be valid for wrapped endotracheal tubes of other sizes. Nevertheless, I encourage testing of the foil-wrapped endotracheal tube with the laser before its use.

Dr. Williamson's suggestions on the degree of overlapping to use when wrapping an endotracheal tube with metallic foil tape are well taken. They should contribute to a smoother external contour of the endotracheal tube.

Mitchel B. Sosis, MD, PhD
Department of Anesthesiology
Rush Presbyterian-St. Luke's Medical Center
Chicago, IL 60612

Reference

1. Sosis MB. Evaluation of five metallic tapes for protection of endotracheal tubes during CO_2 laser surgery. Anesth Analg 1989;68:392–3.

Systemic Droperidol and Epidural Morphine in the Management of Postoperative Pain

Key Words: PAIN, POSTOPERATIVE—epidural droperidol, morphine. ANESTHETIC TECHNIQUES, EPIDURAL—droperidol, morphine.

To the Editor:

In their recent study on the management of postoperative analgesia, Naji et al. (1) found that the addition of epidural droperidol to epidural morphine reduced the incidence and severity of morphine-related side effects. Although a systemic action of droperidol probably could not explain such prolonged effects (which were more likely to be due to direct spinal and supraspinal action), this should not be ruled out before it has been tested. We conducted a study in 40 ASA physical status I patients undergoing elective cesarean section under epidural anesthesia. The patients received 150 mg of 0.5% bupivacaine with epinephrine 1:200,000 and 2 mg of morphine in a single epidural injection, with no supplemental analgesia being required in any case. After delivery, patients were randomly allocated to two different groups of 20 each, one of which received 2.5 mg of intravenous droperidol. Patients had indwelling urinary catheters in place for 4 h after surgery and received supplemental 50 mg of intramuscular diclofenac every 6 h for postoperative analgesia. Patients were visited by a nurse who was blinded to the drugs used 4 and 24 h after the induction of epidural anesthesia to assess quality of postoperative analgesia and morphine-related side effects. All patients were satisfied with the quality of analgesia, and no patient required additional medication in the first 24 h. The incidence of side effects in both groups (Table 1) was compared by testing the difference between two population proportions, considering the data to have a normal distribution. A P value of <0.05 was considered to be statistically significant.

Table 1. Incidence of Side Effects

	With droperidol	Without droperidol
Pruritus 4 h	12/20	15/20
Requiring treatment	3/20	4/20
Pruritus 24 h	15/20	13/20
Requiring treatment	1/20	4/20
Vomiting 4 h	1/20	1/20
Vomiting 24 h	2/20	2/20
Somnolence 4 h	16/20	9/20[a]
Somnolence 24 h	9/20	5/20
Patients requiring urinary catheter	2/19	0/20

[a] $P < 0.05$ compared with the group with droperidol.

The results suggest that the systemic effects of droperidol are of no clinical significance in reducing the side effects of epidural morphine. A direct spinal or supraspinal effect is more likely to be responsible for that.

José Carlos Almeida Carvalho, MD
Roberto Simão Mathias, MD
Waldir Garcia Senra, MD
Marcelo Luis Abramides Torres, MD
Constantin Adam, MD
Alberto Vasconcelos, MD
José Edison de Moraes, MD
Sonia Regina Corrallo, RN
Department of Anesthesiology
University of São Paulo and
Maternidade Pró Matre Paulista
Avenida Macuco 49 Apto 21
04523 São Paulo, Brazil

Reference

1. Naji P, Farschtschian M, Wilder-Smith OL, Wilder-Smith CH. Epidural droperidol and morphine for postoperative pain. Anesth Analg 1990;70:583–8.

ANESTH ANALG 1991;72:417–20

Book Reviews

Obstetric Anesthesia. Anesthesia Clinics of North America, Volume 8, No. 1.

L. S. Reisner, ed. Philadelphia: W. B. Saunders, 1990, 221 pp, $27.00 for single issue or $86.00 for annual subscription.

This issue of the Anesthesiology Clinics of North America deals with 13 select topics of interest in obstetric anesthesia. A particularly noteworthy article is the one entitled "AIDS: Concerns for the Obstetric Care Provider." This is an escalating problem and a concern of great magnitude that we confront in the 1990s. This outstanding article presents the most current information on AIDS including the Centers for Disease Control serologic surveys of AIDS in pregnant women and infants, the diagnostic testing effects of pregnancy on HIV-related disease, and the effects of HIV itself on pregnancy. Furthermore, it addresses the impact of various types of anesthetics and operations on AIDS.

Another article of particular interest that is not normally encountered in standard obstetric anesthesia textbooks is that on oxytocics, tocolytics, and prostaglandins. This article has a comprehensive discussion on the physiology of myometrium and the physiologic and side effects of drugs that have opposing actions on the uterus, namely the oxytocics, prostaglandins, and tocolytics.

Chapters discussing rapidly evolving areas of obstetric anesthesia, such as the one on the pharmacologic aspects of local anesthetic use and anesthetic care of the patient with preeclampsia, include the most current developments in these areas as well as the controversial aspects.

The chapters on anesthesia for uncomplicated vaginal delivery and nonobstetric surgery contain current references. However, the chapters on systemic analgesia in labor and delivery and epidural analgesia for labor and delivery can be obtained from any standard obstetric anesthesia text.

The chapter on anesthesia for cesarean section was of particular interest in that it emphasized the use of local anesthesia for cesarean section. As mentioned by Reisner, the use of local anesthesia for cesarean section is a lost art. This reviewer has used this technique at least twice in the last 4 to 5 years and found it invaluable in dire situations, coupled with a compromised airway. Local infiltration anesthesia is tenable when a midline incision is used, exteriorization of the uterus is avoided, and one has a gentle surgeon.

The chapter on critical care for the pregnant patient was disappointing. This chapter had piecemeal discussions on induced hypotension in the pregnant patient with intracranial aneurysms, hemodynamics in preeclampsia, vasopressors, and vasodilators. The reader will best be served by referring to a text on critical care in obstetric patients.

In summary, this book is not comprehensive but does contain some excellent, up-to-date material on various medical conditions and procedures encountered daily in the obstetric suite.

Maya S. Suresh, MD
Department of Anesthesia
University of Texas Medical School
Galveston, Texas

Fiberoptic Airway Endoscopy in Anesthesia and Critical Care

Andranik Ovassapian. New York: Raven Press, 1990, 172 pp, $105.00.

The incorporation of fiberoptic endoscopy as an essential component of the anesthesiologist's armamentarium is due in no small part to the efforts of Andranik Ovassapian and his colleagues at Northwestern University. This monograph is an additional step in their efforts to popularize the technique. The introductory four chapters deal with the principles of fiberoptic endoscopy, gross and radiographic anatomy of the airway, and a detailed description of topical anesthesia—so essential for successful fiberoptic examination and intubation. Included in the latter chapter is a superficial review of the pharmacology of the applicable local anesthetics. The next three chapters detail the author's extensive experience with fiberoptic intubation of the trachea and the bronchi in the operating suite as well as in the critical care arena.

Explicit directions are provided for the novice in the placement of both single- and double-lumen tubes. High-quality line drawings and photographs of the image viewed through the fiberscope provide basic instruction as well as numerous "tricks of the trade." The chapters on the difficult airway and the difficult intubation illustrate once again the need for all anesthesiologists to be facile with these techniques. If further reinforcement is needed, it is

©1991 by the International Anesthesia Research Society

provided by the 10 case reports that follow. The last chapter, written with the late Michael Dykes who is well known for his interest in education in anesthesia, provides a step-by-step scheme for teaching and learning fiberoptic endotracheal intubation.

The careful reader will be momentarily distracted by the occasional intermingling of inches and centimeters, the use of the singular where the plural is indicated, and the confusion over the similarities between the Carlens, White, and Bryce-Smith double-lumen tubes. These minor flaws, however, do not detract from the overall usefulness of the work. This monograph should be read carefully by any neophyte planning to become familiar with these techniques. The author's admonition: "Unfortunately, self instruction without the guidance of an expert is associated with such a high incidence of failure that many become disenchanted with the technique" must always be borne in mind. No text, no matter how well written and well illustrated can substitute for expert instruction and constant practice.

Howard L. Zauder, MD, PhD
Albuquerque, New Mexico

Envisioning Information

Edward R. Tufte. Cheshire, Conn.: Graphics Press, 1990, 126 pp, $48.00.

What do the following have in common: Japanese weather charts, illustrations from Galileo Galilei's *History and Demonstrations Concerning Sunspots and Their Phenomena,* Mrs. K.'s annotated hospital bill, and a table of the criminal activity of government informants? They are all efficient, data-dense, clear presentations of information and are representative of the wondrous examples from Edward Tufte's newest book *Envisioning Information.* Tufte's earlier work, *The Visual Display of Quantitative Information,* published in 1983, is recognized as a classic in the field of visual presentation of statistical information, and *Envisioning Information* should achieve the same status.

The book is organized into six chapters, the first of which is entitled "Escaping Flatland." Scientists, cartographers, statisticians, and educators attempt to preserve the multidimensional quality of information on the two-dimensional surface of the printed page. Techniques and examples for avoiding one-dimensional or two-dimensional data display (flatland) are the basis of the first chapter and form the central thrust of the book as a whole. Data can have a multidimensional richness that has nothing to do with unnecessary adornment or "chartjunk." Tufte reemphasizes an important theme from his earlier work: if the data are so uninteresting as to need diversionary window dressing, then the author has the wrong data.

"Macro/Micro Readings," the subject of Chapter 2, describes the overall effect (macro reading) of an illustration and the clarifying effect of minute detail (micro reading). The usual design approach to graphic information is to delete detail and to simplify. Tufte advocates an unconventional approach, which is "to clarify, add detail." Chapter 3, the "Layering and Separation" of elements, is a beautiful demonstration of "What matters—inevitably, unrelentingly—is the proper relationship among information layers." The thickness of line, the choice of color, and the choice of type style, size, and weight all can serve to enhance or destroy a table or a figure. In an example drawn from medicine, the improvement in the readability of an electrocardiogram is marked when the grid of the recording paper is changed from heavy black lines to a toned-down grid. The grid stays in the background (layering), and the tracing emerges (separation) with added clarity.

Chapters 4, 5, and 6 describe more advanced design strategies, many of which will be surprisingly familiar to the physician. The chapter entitled "Small Multiples," for example, elaborates the differences between objects or changes with time by repeating the design under differing conditions. For example, dozens of images from a CT scan can be readily interpreted once the viewer is oriented and understands the progression of the slices.

Envisioning Information is more general in its scope and less limited to statistical information display than Tufte's earlier work. It does, however, provide the scientist/reader with a useful framework for planning the display of data. Each page demonstrates clarity of design, legibility, and readability. Although many figures would not fare well if translated unmodified to 35-mm slides, the graphic examples shine when printed on paper because they are meant for close scrutiny. Whether examined closely or merely skimmed, this book is quite simply a joy to read and is a worthy companion to *The Visual Display of Quantitative Information.*

Mark S. Schreiner, MD
Children's Hospital of Philadelphia
University of Pennsylvania
Philadelphia, Pennsylvania

Postanesthesia Care Unit Problems. Anesthesiology Clinics of North America, Volume 8, No. 2.

G. Shapiro, ed. Philadelphia: W. B. Saunders, 1990, 217 pp, $69.00.

Quality assurance should apply to books as well as to clinical care, and this monograph is a prime example of the need for quality assurance techniques. Although the guest editor describes the central theme of this book as the management of postanesthesia problems, and although understanding problems is the key to preventing harm and protecting the patient, and although the statement is made, "No sensible choice of patient management can be made without careful analysis of the advantages and disadvantages of each course of action," the quality of care taken with this text is substandard.

One problem with this book is its unevenness, not uncommon in multiauthored, multiinstitutional texts. Two chapters—The Management of Fluid and Electrolyte Problems, and Ventilatory and Pulmonary Management—provide background material more appropriate to a surgical or medical intensive care unit. Once more specialized subjects, such as the obstetric recovery room, postanesthetic pediatric problems, and ambulatory surgery postanesthesia care units (PACUs) are discussed, the writing becomes more targeted, focused, and useful. The opening chapter on PACU administration and staffing is a helpful overview but misses one crucial element: transfer of authority from anesthesiologist to PACU nurse. The chapter on ventilatory and pulmonary management reads like a medical intensive care unit text, inappropriate for anesthesiologists and PACU nurses in a short-term recovery room environment. Very little information is presented on the airway and respiratory problems commonly encountered in the PACU. Essentially no information is presented concerning the effects of residual anesthesia on postoperative respiratory depression or hypoxic ventilatory drive, yet two and a half pages are devoted to the subject of aspiration pneumonia, fortunately a rare event in the operating room and even rarer in the PACU. Although the authors mention the need for pulse oximetry in the PACU, they refer to an operating room study of pediatric patients to justify this statement. Finally, the authors describe three types of respiratory failure: type III is known as *perioperative respiratory failure* and is characterized by low Po_2 associated with and partly caused by an elevated $Paco_2$. This description is referenced to the *Proceedings of the Fourth World Congress on Intensive and Critical Care Medicine, 1985*—a clearly outdated, not refereed, nor even a widely available publication.

On the other hand, the chapter on the obstetric recovery room is a well-written, concise, useful treatise, particularly for those not familiar with obstetrical recovery rooms or for those who deal infrequently with obstetrical patients.

The management of postanesthesia pediatric problems is quite complete, yet contains numerous errors, e.g., an extrinsic muscle of the larynx is called a thyroid muscle, the statement that "weaning from ventilatory support should include blood gases which are stable with an Fio_2 of less than 0.5 and an arterial Po_2 of more than 6 mm Hg," and many incorrect references. When discussing placement of endotracheal tubes, no mention is made of the new, noninvasive endotracheal tube locator. On the subject of allowable whole blood loss in pediatric surgical patients, the author states that one should obtain a final postoperative hematocrit of not less than 30% for infants and children and 40% for premature infants and newborns, and this is referenced to a 1977 article. Yet no commentary is offered on this statement. This chapter, in particular, contains more spelling errors than the others, but the most egregious error is that many of the references are incorrectly numbered. Dogmatic and controversial statements that the reader might wish to investigate do not correlate with the reference number indicated.

Discussion of neurosurgical patients in the PACU is superficial and full of platitudes, offers little additional knowledge, and is loaded with bibliographic errors. The coauthor's name of the legal chapter within this book is misspelled within the bibliography of the neurosurgical chapter.

Two chapters concerning hypothermia and hyperthermia are models of excellence, particularly the concise, declarative, and informative chapter on diagnosis and treatment of hyperthermia in the PACU. However, no mention is made of the value of peripheral venous blood gases in diagnosing malignant hyperthermia, although arterial blood gases are said to be very useful in supporting the diagnosis. What could have been a useful chapter on problem management in the ambulatory surgery PACU contains many dogmatic statements, such as one advocating the use of narcotics to *reduce* the incidence of nausea and vomiting in the PACU. Unfortunately, this chapter, which ends with 20 references, has no numbered references within the text to which the reader can refer to document the author's controversial statements.

In an important chapter, Pain Management in the PACU, the authors discuss narcotic loading in the operating room as a useful approach to postoperative analgesia. They do not mention the profound respiratory depression that can occur within the PACU in patients who are unusually sensitive to narcotics or who, when receiving narcotics in combination with numerous other drugs administered intraoperatively, breathe ineffectively in the early postoperative period. This reviewer takes issue with the authors' statement that major side effects of respiratory depression and oversedation from narcotics are rarely seen in the acute postoperative setting if patients are carefully watched over a reasonable period of time. Too many cases of respiratory, then cardiac arrest, occur within the first hour of the PACU in patients who were "awake and responsive" on admission to the PACU. No mention is made of intercostal blocks for postoperative pain relief, particularly after thoracotomies, although a section on intrapleural analgesia is included. In general, the fluid and electrolyte chapter covers information well beyond the time frame of the PACU.

Finally, the chapter on legal problems in the PACU is an interesting exposition on problems of authority, patient management, and triage from a case-law point of view. This chapter does contain some information on transferring responsibility to PACU nurses when the anesthesiologist leaves the PACU after admitting the patient.

Many PACU problems are not discussed or only mentioned in a specialized context. For example, the subject of hypertension, a most common PACU problem, is not covered except as it pertains to neurosurgical patients, certainly not generalizable to the normal adult PACU population. Hypotension and hypovolemia are only covered in the chapter on obstetrical recovery. Except for a few chapters (some of which still contain significant flaws), this book does not provide the reader with a quality product to which he or she is entitled.

David J. Cullen, MD
Harvard Medical School
Massachusetts General Hospital
Boston, Massachusetts

Clinical Applications of Ventilatory Support

R. R. Kirby, M. J. Banner, and J. B. Downs, eds. New York: Churchill Livingstone, 1990, 546 pp, $69.95.

Clinical Applications of Ventilatory Support will serve anesthesiologists and the critical care community as both a reference text and a book for practical application in the intensive care unit or the operating room. It is especially cogent for the practice of anesthesiology in that many of the chapters include equipment considerations and principles that are applicable in these two areas. The book includes discussions of operating room ventilatory equipment and special ventilatory problems in the operating room. There is some overlap between chapters, for example, with ventilatory classification schemes and discussions of flow and pressure generators for the ventilators. Because the various chapters discuss different aspects of these topics, their redundancy is not great. However, there is no cross-referencing between chapters within the text itself, although the index does include reference to all pages for a single topic discussed in several places.

The introduction of this book is interesting in and of itself. The discussion begins in Vesalius' time (mid-1500s) and proceeds to current ventilatory principles and applications. The chapter is entertaining if not educational reading. Although there are many excellent chapters, three of particular value to the anesthesiologist will be mentioned.

The chapter on ventilation during anesthesia distinguishes this book from others on ventilatory support. The equipment in the operating room versus the intensive care unit is discussed in some detail; there is also a major section on anesthesia ventilators. Anesthesia breathing circuits and the interaction between the anesthesia machine and the ventilator receive detailed attention. These sections focus on delivering ventilatory support rather than on delivering anesthesia.

The chapter on medicolegal considerations is an excellent review of landmark cases and quotes decisions handed down mostly from higher courts. The discussion is divided into clinical situations based on competency of the patient, terminal disease, living well, and "do not resuscitate orders." Further, the chapter discusses seeking judicial ruling and informed consent. This chapter should probably be read by every medical student. It is a succinct review of medicolegal considerations for one narrow but important part of medicine. The well-organized approach demonstrates principles of dealing with medicine and the law.

The penultimate chapter discussed the ventilators themselves, is over 100 pages long, and appears to be a condensation of the same editors' book on mechanical ventilators. There are excellent schematic drawings of a variety of marketed ventilators with lucid discussions of controls, operation, monitors/alarms, and safety features.

Clinical Applications of Ventilatory Support is an excellent text and reference book. It is carefully edited and should serve both as a refresher and reference for the seasoned practitioner and as an excellent text for senior-level residents.

M. Christine Stock, MD
Emery University
Atlanta, Georgia

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Alderson JD, Frost EAM. *Spinal Cord Injuries. Anaesthetic and Associated Care.* Stoneham, Mass.: Butterworth-Heinemann, 258 pp, $70.00.

Datta S, ed. *Anesthetic and Obstetric Management of High-Risk Pregnancy.* St. Louis: Mosby Year Book, 1990, 719 pp, $79.00.

Estafanous FG, ed. *Opioids in Anesthesia II.* Stoneham, Mass.: Butterworth-Heinemann. 1990, 331 pp, $45.00.

Hare BD, Fine PG, eds. *Chronic Pain.* Volume 4, No. 4 in Problems in Anesthesia Series. Philadelphia: J.B. Lippincott, 1990, 137 pp, $30.00 single issue or $65.00 annual subscription of four issues.

Mumenthaler M, Van Zwieten PA, Farcot JM, eds. *Treatment of Chronic Pain: Possibilities, Limitations, and Long-Term Follow-up.* New York: Harwood Academic Publishers, 1990, 337 pp, $95.00 hardback, $63.00 paperback.

Stene JK, Grande CM, eds. *Trauma Anesthesia.* Baltimore: Williams & Wilkins, 1990, 510 pp, $79.00.

CO-INDUCTION OF ANESTHESIA

A synergy of effects and advantages

Co-induction—when two or more agents rather than one are used for induction—may offer clinical benefits if there is anesthetic synergy. Specifically, subanesthetic doses of each agent may produce a prompt, short-acting effect with more stable hemodynamics than one agent alone.[1]

A classic example of synergy is mutual enhancement of receptor-site affinity: *e.g.*, a benzodiazepine such as VERSED may alter barbiturate receptors in a way that enhances barbiturate effects. Likewise, a barbiturate may potentiate a benzodiazepine by acting at its receptor sites.[2,3]

Lower doses of both agents

Several studies have shown that a small initial dose of VERSED will allow lower induction doses of thiopental, methohexital, fentanyl, alfentanil or ketamine.[1,4-9]

In one study of 90 unpremedicated ASA Class I & II patients, co-induction with VERSED followed by thiopental required just 1/4 of each drug's usual ED_{50}.[5]

Lower risk of breakthrough awareness

VERSED produces a marked amnestic effect. Therefore, a VERSED co-induction may reduce the possibility of recall (*e.g.*, during intubation) in the event of lightening of anesthesia with short-acting hypnotics such as thiopental or propofol.

Dosing considerations with VERSED® (midazolam HCl/Roche)©

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.*, drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

IDEAS IN ANESTHESIA

■ ■ ■ ■ ■ ■ ■ ■

AN ONGOING SERIES

Please see summary of product information on following page.

References: 1. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology.* 1990; 73(3A):A1216. **2.** Skolnick P, *et al.* Pentobarbital: dual actions to increase brain benzodiazepine receptor affinity. *Science.* March 1981;211:1448-1450. **3.** Miller LG, *et al.* Acute barbiturate administration increases benzodiazepine receptor binding in vivo. *Psychopharmacology (Berlin).* 1988;96:385-390. **4.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction—thiopental, ketamine and midazolam. *Anesthesiology.* 1982;57:279-284. **5.** Tverskoy M, *et al.* Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg.* 1988;67:342-345. **6.** Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth.* 1989;63:109-112. **7.** Kissin I, *et al.* Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg.* 1990;71:65-69. **8.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg.* 1989;69:213-217. 9. Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth.* 1990;64:45-47.

VERSED®
(brand of midazolam HCl/Roche)ⒸIV
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

Roche Laboratories
a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

Classified Advertising

ILLINOIS
Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad-based practice. All surgical subspecialties represented. Minimal OB and pain management. Early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 61614.

511J/C

CALIFORNIA
From time to time faculty positions as an Assistant Professor become available in the *Regular Professorial Series (Tenure Track)* in the UCLA Department of Anesthesiology. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills; commitment to discovery; eligibility for a California Medical License; ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

526J/C

CALIFORNIA
Faculty positions in the *Clinician-Teacher* Academic Professorial Series in the UCLA Department of Anesthesiology are available. We are interested in all anesthesia subspecialties. Requisites include eligibility for a California Medical License and ABA certification or in process. Address correspondence with five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

527J/C

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology of Columbus Children's Hospital is expanding its fellowship program. Positions are currently available for a 1-year fellowship in pediatric anesthesiology. Children's Hospital of Columbus, Ohio is a 313-bed general pediatric institution with a surgery caseload of 13,000–14,000 cases per year. All pediatric surgical specialities are represented with large case loads in pediatric neurosurgery and cardiovascular surgery. Regional anesthesia in infants and children along with acute/chronic pain management experience is available. An active transplantation service is present. Opportunity for research is provided under the guidance of a full-time director of research. Inquiries should be submitted to J. David Martino, MD, Chairman, Department of Anesthesiology, Columbus Children's Hospital, Columbus, OH 43205.

531K/D

MISSOURI
The Department of Anesthesiology of St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.

544L/E

MAINE
BC or BE MD to join group of three MD anesthesiologists and four CRNAs, in the practice of anesthesia, intensive care and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.

560L/E

ANESTHESIOLOGIST
BC/BE to join group of 10 MDs with CRNAs in a large hospital located in a pleasant midwestern community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and OB. Excellent starting salary and benefits package leading to early partnership. Send CV to Associated Anesthesiologists of Toledo, Inc., 2409 Cherry Street, Suite 4, Toledo, OH 43608.

566A/C

LOCUM TENENS
Anesthesiologist, MD. Experienced, AMG, board certified. Will consider permanent situation. Licensed: MO, KS, CO, IA, NC, SC, PA, VA, IL, IN, KY, OH, TN; others pending. PO Box 1176, Kings Mountain, NC 28086; (704) 739-4683 Office, (704) 739-1917 Home.

568A/C

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

571A/F

SOUTHERN CALIFORNIA
Olive View Medical Center, a UCLA-affiliated Los Angeles County hospital, is seek-

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announcements, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum ¼ page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

ing academically qualified anesthesiologists. Board certified or in process required. Training in OB, pediatrics, or neuro desired. No OH or trauma. Please send CV with three references to Anesthesia Search, Department of Anesthesiology, Olive View Medical Center, 14445 Olive View Drive, Sylmar, CA 91342. Equal Opportunity Employer.

573A/C

ILLINOIS, CHICAGO
Anesthesiologist BC/BE to join expanding group practice limited to outpatient anesthesia. Excellent opportunity for growth. Send CV to Marc Sloan, MD, 25 East Washington, Suite 300, Chicago, IL 60602.

574A/F

WANTED?
Affable anesthesiologist to join progressive fun-loving department in central Vermont area. Locate in the mountains. See the leaves. 4 MD, 1 CRNA group. We do pain our way. DO IT NOW—send CV to Chairman, Department of Anesthesia, c/o Central Vermont Hospital, PO Box 547, Barre, VT 05641. A limited time offer. Respond now!!

580A/D

CALIFORNIA
The UCLA Department of Anesthesiology has openings for faculty with experience in anesthesia for organ transplantation. Requisites include clinical and teaching skills; eligibility for a California medical license; ABA certification or in process. Address correspondence with names of five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

584A/F

THE UNIVERSITY OF NEW MEXICO
A reorganized, expanding Department of Anesthesiology in the "Land of Enchantment" has seven immediate openings at the Assistant and Associate Professor levels. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to James C. Scott, MD, Associate Professor and Acting Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106, (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

585A/F

Cardiac anesthesiologists and Director of Obstetric Anesthesiology sought for academic medical center practice. Candidates for obstetric position must have experience in all types of obstetric anesthesia. Interest in research and teaching highly desirable. Present staff of 25 MDs, over 40 CRNAs, and over 20 residents provides challenging anesthesia care team setting. OR area contains state-of-the-art equipment in 20 new or renovated suites. Interested applicants should send CV and three references to: Dr. Philip Lumb, Professor and Chairman, Albany Medical College, Department of Anesthesiology, Code A-131, Albany, NY 12208. EOE

592B/F

WISCONSIN
Anesthesiologist BC/BE to work with four MDs in 200+ bed hospital and surgicenter midway between Milwaukee and Chicago. Fee for service. Send CV and references to Dr. I. Romana, PO Box 594, Kenosha, WI 53141.

597B/E

INDIANA
Faculty positions are available at all academic ranks for adult anesthesia. Positions include teaching and administrative responsibilities as well as opportunities to pursue research interests. Experience in pain management and organ transplantation is desirable. All candidates must be board certified or board eligible. Individuals appointed to the tenure track will be required to maintain an active and ongoing research program. Please send curriculum vitae to Robert K. Stoelting, Professor and Chairman, Department of Anesthesia, Indiana University School of Medicine, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115. Indiana is an equal opportunity employer.

599B/D

OREGON
Fellowship—Pain Management. July 1991 and July 1992 Fellowship positions available for physicians who have completed clinical anesthesia training. Setting is a multidisciplinary pain management center that deals with the entire range of acute and chronic outpatient and inpatient pain problems. Experience offered in most diagnostic and therapeutic procedures including intraspinal narcotics and stimulators, cryo, regional blockade, PCA. An active research program exists and participation by fellow is encouraged. Please send CV and names of three references to Wendell C. Stevens, MD, Chairman, Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

600B/D

NEW HAMPSHIRE
Excellent opportunity for BC/BE anesthesiologist to join two-person group. Surgical cases include OB/GYN, urology, ENT, ophthalmology, Peds, Ortho, and vascular and general surgery. Position open due to enormous growth in surgical base. Partnership position includes competitive compensation and benefit package. NH is a tax-free state that enjoys year-round recreational and cultural opportunities. This position combines a challenging practice with a quality lifestyle that is rare in this age of corporate medicine. For additional information call or write: Martin Rosenberg, Director of Professional Services, Valley Regional Hospital, 243 Elm Street, Claremont, NH 03743; (603) 543-1606.

601B/D

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO is recruiting for five faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol-driven human studies. The four other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the five positions may be tenured track. Otherwise the positions are non-tenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology and a California medical license is required. Possession of a certificate of special qualifications in critical care medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego is an equal opportunity/AA employer. All applications received by April 30, 1991 will receive thorough consideration.

603B/D

Two full-time faculty positions at the Assistant/Associate/Full Professor level. The position requires abilities appropriate for a University position. Applicants must be board eligible and meet California license requirements. Responsibilities include instruction in the various aspects of anesthesiology; clinical service; clinical and/or basic science research; and publication of scholarly articles. Send curriculum vitae, bibliography and *names of three to five (3–5) references* to Gerald Gronert, MD, Professor and Acting Chair, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until April 30, 1991. We are an Equal Opportunity/ Affirmative Action Employer.

609BC

Tertiary care hospital in Cleveland, Ohio currently seeking BC Division Director to join group of four anesthesiologists, directing nine anesthetists through a team approach. Surgical schedule includes OHS, trauma, minimal pediatrics, no OB. Send CV to Aldona T. Lyon, MD, Acting Director, Division of Anesthesiology, Saint Vincent Charity Hospital and Health Center 2351 East 22nd Street, Cleveland, OH 44115.

610CD

VIRGINIA

Group of eight anesthesiologists at two community hospitals looking to immediately expand. Positions available for BC/BE anesthesiologists in the Tidewater Virginia. Beautiful area on the Chesapeake Bay, excellent for families. Managing CRNAs. No open-heart, some pain experience favored. A. Goldman, MD, 21 River View Drive, Poquoson, VA 23662.

611C

PLANNING TO RETIRE AND MOVE TO FLORIDA—WHY WAIT?

Established group looking for anesthesiologist who would like to spend a few practice years before retirement in a Florida Gulf Coast Outpatient Specialty Clinic supervising one CRNA. Working conditions are a relaxed and pleasant day job (no nights, weekends, holidays) with no administrating or office responsibilities. If practice hassles, high stress cases, and call responsibilities are getting to be too much, this one is for you. Area offers outstanding outdoor activities, professional sports and cultural events. Must have a Florida license. Reply to Box 612CD.

612CD

FLORIDA

Central Florida Area—Excellent opportunity for MD with fellowship or extensive clinical experience in chronic pain management. Salary to partnership. Reply Box 613C/E.

613C/E

BE/BC ANESTHESIOLOGIST

SW PA, 300-bed, modern community hospital to work with 3 MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to box 614C/F.

614C/F

MASSACHUSETTS

BC or BE anesthesiologist or CRNA to join group of five anesthesiologists to work in suburban hospital north of Boston. Hospital performs approximately 6000 surgical procedures per year. 24-Hour OB coverage. Excellent salary and benefits. On-site day care. Send CV to S.R. Meka, MD, 5 Woodland Road, Stoneham, MA 02180 or call at (617) 979-7000, extension 2826.

615C

KENTUCKY

The Department of Anesthesiology, University of Louisville School of Medicine, Louisville, Kentucky has an opening for a BC/BE anesthesiologist. As a faculty member you will be provided the opportunity to fulfill the learning requirements of the 36 residents within our program.

The University of Louisville School of Medicine offers competitive salaries and fringe benefits. Applicants please send curriculum vitae to B. M. Rigor, Sr., MD, Chairman, Department of Anesthesiology, University of Louisville, Louisville, KY 40292. The University of Louisville is an Affirmative Action, Equal Opportunity Employer.

617C

MINNESOTA: MEDICAL DIRECTOR OUTPATIENT ANESTHESIA

Excellent opportunity for an experienced anesthesiologist to join a single specialty group of nine. Medical Director will assist in planning and development of new ambulatory care facility at the Saint Cloud Hospital. Saint Cloud Hospital is a 489-bed regional medical center serving an area of 440,000 Central Minnesotans. Duties will include at least 80% outpatient anesthesia. Qualifications: board certification with strong interest and experience in outpatient anesthesia. Good interpersonal and organizational skills required. This position offers a competitive salary, excellent benefits, and limited call duty. St. Cloud is a rapidly growing area of 100,000 people located 70 miles northwest of Minneapolis/St. Paul. A clean safe city, St. Cloud offers three universities, a wide variety of cultural and recreational opportunities, and an ideal family environment. Please send CV to John Schnettler, Physician Recruiter, Saint Cloud Hospital, 1406 6th Avenue North, St. Cloud, MN 56303; 1-800-289-6654.

618CD

UTAH

The University of Utah seeks board-certified and/or board-eligible anesthesiologist for appointment at instructor to associate professor level. Emphasis is given to promising or established individuals with expertise in obstetrical anesthesia. Research experience and/or productivity is necessary. Send curriculum vitae to K.C. Wong, MD, PhD, Chairman, Department of Anesthesiology, University of Utah Health Science Center, 50 North Medical Drive, Salt Lake City, UT 84132. Equal Opportunity/ Affirmative Action Employer. Closing Date: March 31, 1991 or until qualified candidate identified.

619C

ANESTHESIOLOGIST

Sinai Hospital, an acute-care teaching hospital, in northwestern Detroit seeks a qualified anesthesiologist who is board certified or in the exam process. Salary will be commensurate with experience. The candidate will be expected to participate actively in both undergraduate and resident education. Send CV to Mark McNash, Administrative Director, Sinai Hospital, 6767 West Outer Drive, Detroit, MI 48235. An equal opportunity employer.

620CD

FLORIDA

BC/BE Anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/H.

621C/H

PAIN FELLOWSHIP

Expanding Pain Management Center of Medical College of Georgia has opening for Pain Fellow starting July 1991. Choice of 6 or 12 months at competitive salary. Setting is interdisciplinary, with focus on return to functionality. Busy nerve block clinic, acute pain service with PCA and epidural analgesia, cancer pain management, and tertiary region-wide referral of large variety of complex diagnostic challenges. Growing pediatric pain program, including postop, oncology, and sickle cell crisis. Applicant must have completed residency training in anesthesiology, be board eligible, and have Georgia license. Clinical research encouraged. The Fellow supervises two residents plus one student; adequate management exposure to direct a pain service on completion. Augusta is a clean, pleasant university town near huge lake for boating, and a few hours from Atlanta, beach, and mountains.

Inquires to Rudolph H. de Jong, MD, (404) 721-PAIN, application packet from Susan W. Dawkins, Department of Anesthesiology, Medical College of Georgia, Augusta, GA 30912-2700. EEO/AA Employer.

622CD

PENNSYLVANIA

Immediate opening for BC/BE anesthesiologist to join 2 MDs and CRNAs in PA. Fee for service. Call Dr. Shah, (717) 242-7186, 9 AM to 5 PM.

623CD

ILLINOIS

Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approx. 40,000 (35 mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 624C/H.

624C/H

ALABAMA—ANESTHESIOLOGIST

Faculty position for clinical BC/BE anesthesiologist at University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical research, variety of clinical cases including liver transplantation. Desire to participate in teaching necessary. Limited night call. Generous benefit package. Salary competitive with private practice situations. Located in downtown Birmingham; city rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by *Newsweek*, February 1989, as "one of the nation's top 10 hot cities." Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205)934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

626C/F

DIRECTOR, PAIN MANAGEMENT SERVICE

The Department of Anesthesiology at the Oregon Health Sciences University is recruiting for a Director of our Pain Management Service. The Service encompasses management of acute and chronic pain, training of medical students, residents, and fellows and research. The Service provides a multidisciplinary approach to pain control and has vigorous clinical psychology and neuroimplant components. Excellent interdisciplinary relationships exist with neurosurgery, orthopedics, and surgical oncology. Board eligibility in anesthesiology or equivalent certification plus training and/or experience in pain management are required. Research experience and evidence of productivity are desired. Academic rank for successful candidate will be determined by qualifications. Candidate must be eligible for Oregon medical license.

Please send curriculum vitae and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, OHSU, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an equal opportunity/affirmative action employer.

627C/E

ILLINOIS

Anesthesiologist BC/BE sought for MD/CRNA team at progressive 350-bed southern Illinois hospital which includes cardiothoracic. CV to Box 587AC.

587A/C

MONTANA

Northwestern Montana Rockies. Seeking BC/BE anesthesiologist to join other anesthesiologist to provide coverage for a 44-bed community hospital in this Montana resort community. Located near Glacier National Park, Big Mountain Ski Resort, Flathead Lake, and numerous championship golf courses. An opportunity for someone longing for an experience in an unspoiled environment. Please send CV or call Marcel Loh, Administrator, North Valley Hospital, 6575 Highway 93 South, Whitefish, MT 59937; (406) 862-2501, ext. 250.

630C

FULL-TIME ANESTHESIOLOGIST

BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to Lake Charles Anesthesiology, 1415 18th Street, Lake Charles, LA 70601.

634C/H

PAIN PRACTICE FOR SALE

in beautiful Santa Fe, New Mexico, the Land of Enchantment. Well-established practice, treating acute and chronic pain. Specializing in injection procedures, Dr. Klinghardt, (505) 983-3891.

625C

DANIEL & YEAGER LOCUM TENENS

Daniel & Yeager is the only name you need for locum tenens. Anesthesia is our exclusive specialty, so you are assured of our undivided attention. Earn a premium income while eliminating administrative headaches and malpractice premiums, we cover it all. Call 1-800-955-1919 or write to PO Box 2065, Huntsville, AL 35804-2065.

629C/H

LOCUM TENENS

Locum tenens anesthesiologists. Earn up to $200,000.00 per year. Don't work for an agency. Work for yourself. For details, send name and address to Dr. Monroe, 7035 Hwy 6 South, Suite #175-B, Houston, TX 77083.

616C/F

A WEEKEND OF PRACTICE ORAL EXAMS

Practice exams, not lectures. We are the original course in this format. 20 hours category I CME credit, two board-certified instructors, 12 students maximum. Dallas, March 22–24; Denver, April 5–7. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617. (419) 843-4480.

559C

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:

The unique feature of these tutorials is the small group size. The personalized format with a maximum of four students in a session allows your performance to be evaluated throughout the session and permits you to raise questions for discussion. Tutoring for the written and oral exams are given separately. The sessions are held in San Francisco and New York and are given in blocks of 3 days. FOR THE WRITTENS, essential test-taking skills are taught for dealing with multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, mock orals are practiced using the guided case discussions which meet the Board's stated objectives. All students will receive study programs for use following these sessions. CALL 415-321-1117.

628C/H

J. STEPHENS MAYHUGH AND ASSOCIATES LOCUM TENENS ANESTHESIA SERVICES

Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

552L/E

DON'T FAIL THE WRITTEN BOARDS/ITE

New 1990 edition of practice questions (including past board remembered questions), answers, test-taking techniques, and more. We want to help you pass. Order the original, MEDTEXT call 1-800-695-6301 24 hours a day.

590A/F

(800) FAST-GAS

The number that hundreds of hospitals nationwide have called for permanent and temporary anesthesia services. The number that thousands of anesthesia professionals have called to secure permanent and temporary positions nationwide. Bay Area Anesthesia, Inc. 1-800-327-8427 for years of professional anesthesia service.

582B/G

Dial 1-800/RENT-A-DOC

For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-0800/736-8236 * PO Box 640 * Michigan City, IN 46360.

598B/L

FOR SALE

Two 30/70 Proportioner Anesthesia Machines by OHIO with Ethrane, Forane and Halothane TEC 4 vaporizers, CO_2 absorbers and O_2 monitors. Stock #216-7193-800; Serial #BCFM00081/BCFM00090. Six years old with very little use—LIKE NEW. $10,000 each. Quarterly maintenance by Bill Turner, Ohmeda technician. May contact Mr. Turner for reference concerning these machines at 1-800-433-5070. If interested contact Melinda M. Prevost, MD, (504) 767-2417.

604BC

INDEX TO ADVERTISERS

Anaquest
  Stadol . . . . . A11 thru A12
Arrow International
  Medical Division . . . . . Cover 3
Augustine Medical
  Bair Hugger A6
Burron Medical Inc.
  Spinoscan Spinal Anesthesia Products A28
Cook County Graduate School of Medicine
  Recruitment A18
Halocarbon
  Halothane A12
Janssen Pharmaceutica
  Alfenta A4
  Sufenta A27
Medfusion Inc.
  Syringe Pump A2
Mercury Medical
  2001 Laryngoscope A17
Northern Health Systems
  Computer System A8
Ohmeda
  Rascal II . . . . . Cover 4
Organon Pharmaceuticals
  Norcuron . . . . . Cover 2, A1
Osler Institute
  Course A26
Pan-Pacific Surgical Association
  Meeting A18
Physician Services of America
  Recruitment A18
Preferred Physicians Mutual
  Insurance A13
Professional Seminars, Inc.
  Seminar A17
Hoffman La Roche
  Versed . . . . . A29 thru A30, A14 thru A16
Stuart Pharmaceuticals
  Diprivan . . . . . A19 thru A25
University of Massachusetts Medical Center
  Recruitment A18

Advertising Office: Pharmaceutical Media, Inc., 440 Park Avenue South,
14th Floor, New York, New York 10016. Telephone: (212) 685-5010

UCM (Clinical)
Acc/P

ISSN 0003-2999
Volume 72, Number 4, April 1991

Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In neuromuscular blockade

Norcuron®

(vecuronium bromide) for injection

Minimizes the variables

CARDIOVASCULAR EFFECTS

▽ Cardiovascular stability, even in elderly patients, and in patients with cardiovascular disease[1,2]

HISTAMINE SIDE EFFECTS

▽ NORCURON® requires no dosage adjustments to avoid histamine release

METABOLIC CONSIDERATIONS

▽ May be used safely in patients with renal impairment, and in patients with mild to moderate hepatic impairment[3,4]

As with all drugs in this class, NORCURON® should be administered by adequately trained individuals familiar with its actions, characteristics and hazards.

There for the routine...
There for the unexpected

See following page for brief summary of prescribing information.

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockage beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min) 0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution

†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug	Patient Weight – kg						
µg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

References:

1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983;58:438-440.
2. Lowry KG, Mirakhur RK, Lavery GG, et al: Vecuronium and atracurium in the elderly: A clinical comparison with pancuronium. *Acta Anaesthesiol Scand* 1985;29:405-408.
3. Miller RD, Rupp SM, Fahey MR, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron.* Amsterdam, Excerpta Medica, 1983, pp 124-126.
4. Bell CF, Hunter JM, Jones RS, et al: Use of atracurium and vecuronium in patients with oesophageal varices. *Br J Anaesth* 1985;57:160-168.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Manufactured for ORGANON INC.
By BEN VENUE LABORATORIES, INC. • BEDFORD, OHIO 44146
or by
ORGANON INC. • WEST ORANGE, NEW JERSEY 07052

PTD. IN USA-440, 441 ©1989 ORGANON INC. 5310117

SECOND

AMERICA-JAPAN ANESTHESIA CONGRESS

January 19-21, 1992
Sheraton Waikiki Hotel
Honolulu, Hawaii

The Second America-Japan Anesthesia Congress will present refresher courses and updates by experts from Asia and North America on subjects pertaining to cardiovascular anesthesia, clinical pharmacology and pain management.

Deadline for submission of 15-minute free papers is June 30, 1991

A number of Professor Futami Kosaka Awards will be granted to the best free papers accepted for presentation.

Hotel reservations must be made by December 18, 1991

Registration fee: $250

For further information:
K.C. Wong, M.D., Ph.D. or Vicky Larsen
Department of Anesthesiology
University of Utah School of Medicine
50 North Medical Drive
Salt Lake City, Utah 84132
(801) 581-6115 or 581-4367 FAX

Anesthesia and Analgesia

Official Journal of the International Anesthesia Research Society

Editor-in-Chief
Ronald D. Miller, MD
San Francisco, California

Associate Editor-in-Chief
John H. Tinker, MD
Iowa City, Iowa

Editorial Board

David R. Bevan, MA, MB, BChir
Montreal, Quebec, Canada

Thomas J. Gal, MD
Charlottesville, Virginia

Edward D. Miller, Jr, MD
New York, New York

Nathan L. Pace, MD
Salt Lake City, Utah

Richard J. Palahniuk, MD
Minneapolis, Minnesota

John Savarese, MD
New York, New York

Walter S. Nimmo, MD, BSc, FRCP, FFARCS
Edinburgh, Scotland

Section Editors

Cardiovascular Anesthesia
Joseph G. Reves, MD, Durham, North Carolina

Ambulatory Anesthesia
Patricia Kapur, MD, Los Angeles, California

Neurosurgical Anesthesia
Donald S. Prough, MD, Winston-Salem, North Carolina

Obstetrical Anesthesia
Mieczyslaw Finster, MD, New York, New York

Regional Anesthesia and Pain Management
Phillip O. Bridenbaugh, MD, Cincinnati, Ohio

Pediatric Anesthesia
Paul R. Hickey, MD, Boston, Massachusetts

Critical Care
Ronald G. Pearl, MD, PhD, Stanford, California

Book Review Editor
Norig Ellison, MD, Philadelphia, Pennsylvania

Managing Editor
King Kryger, PhD

Manuscripts and editorial correspondence should be addressed to: King Kryger, PhD, Managing Editor, *Anesthesia and Analgesia*, 3497 Sacramento Street, San Francisco, CA 94118 [telephone: (415) 292-7964; FAX: (415) 292-5157]. For information concerning preparation of manuscripts, see "A Guide for Authors" published quarterly in the Journal.

Books for review should be sent directly to: Book Review Editor, Norig Ellison, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, PA 19104.

Shield against surgical stress

SUFENTA

(sufentanil citrate) Injection CII

For longer more stressful procedures

As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

References: 1. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology. 1982;56:112-118. 2. Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg. 1985;64:897-910. 3. Benefiel DJ, Roizen MF, Lampe GH, et al. Morbidity after aortic surgery with sufentanil vs isoflurane anesthesia. Anesthesiology. 1986;65:A516. Abstract. 4. Roizen MF, Lampe GH, Benefiel DJ, et al. Is increased operative stresss associated with worse outcome? Anesthesiology. 1987;67:A1. Abstract. 5. Clark NJ, Meuleman T, Liu WS, Zwanikken P, Pace N, Stanley TH. Comparison of sufentanil-N_2O and fentanyl-N_2O in patients without cardiac disease undergoing general surgery. Anesthesiology. 1987;66:130-135.

Predictable control of stress responses from induction through recovery

***REDUCES** stress response to intubation and surgical stimulation* ^{1,2}

***PROVIDES** intraoperative hemodynamic stability*

***CONTROL** of the stress response is associated with less postoperative morbidity* ^{3,4}

***MAINTAINS** postoperative analgesia with faster recovery of respiratory drive* ^{5}

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription.
DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with a molecular weight of 578.68. SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.
INDICATIONS AND USAGE: SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.
CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.
WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available. SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.
PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.
Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.
Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.
Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.
Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.
ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.
OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.
DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

world leader in anesthesia research

JANSSEN
PHARMACEUTICA

Piscataway, NJ 08854

March 1986, March 1987
U.S Patent No. 3,998,834
7618505-M

© Janssen Pharmaceutica Inc. 1989 JPI-SU-025A-R

Anesthesia and Analgesia

Volume 72, Number 4, April 1991

Contents

EDITORIALS

Ethics in Publishing *Graham Smith, Ronald D. Miller, Lawrence J. Saidman, and M. Morgan* 421

Glucose Management During Cardiopulmonary Bypass: Cardiovascular and Neurologic Implications *William L. Lanier* 423

SCIENTIFIC ARTICLES

Benefits of a Glucose-Containing Priming Solution for Cardiopulmonary Bypass *Samuel Metz and Arthur S. Keats* 428

Roles of β_1- and β_2-Adrenoceptors in the Mechanism of Halothane Myocardial Sensitization in Dogs *Yukio Hayashi, Koji Sumikawa, Masakazu Kuro, Kazuo Fukumitsu, Chikara Tashiro, and Ikuto Yoshiya* 435

Effects of Halothane on Hypoxic Pulmonary Vasoconstriction in Canine Atelectasis *David H. Johnson, Tom S. Hurst, and I. Mayers* 440

Is Caffeine Withdrawal the Mechanism of Postoperative Headache? *M. Fennelly, D. C. Galletly, and G. I. Purdie* 449

Halothane 1.5 MAC, Isoflurane 1.5 MAC, and the Contractile Responses of Coronary Arteries Obtained From Human Hearts *E. Villeneuve, G. Blaise, J. C. Sill, M. J. Guerard, J. Buluran, and D. Girard* 454

Chronic Verapamil Treatment Depresses Automaticity and Contractility in Isolated Cardiac Tissues *Zeljko J. Bosnjak, Jure Marijic, David L. Roerig, David F. Stowe, V. Shrinivas Murthy, and John P. Kampine* 462

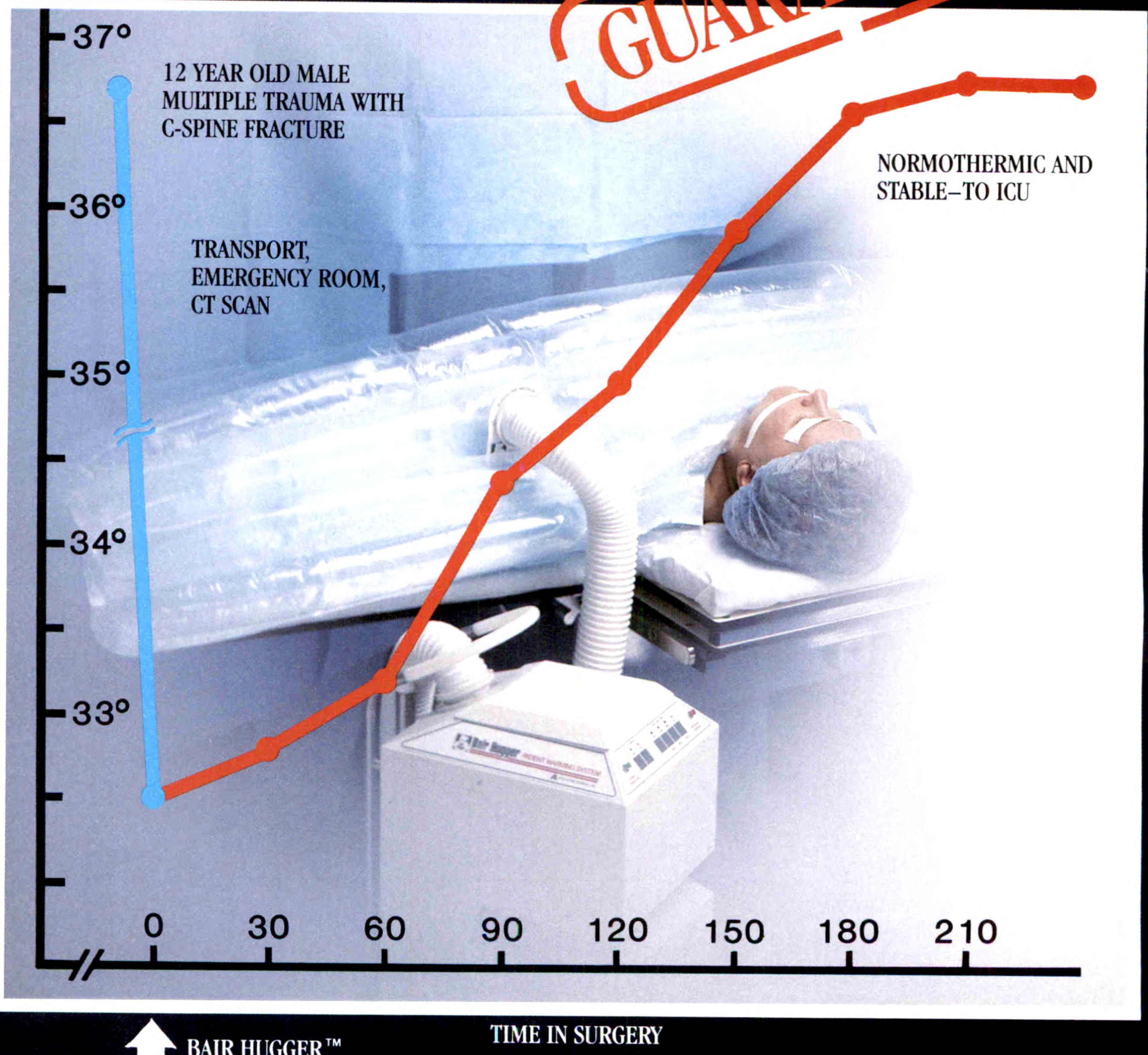
Potentiation of Atracurium Neuromuscular Blockade by Enflurane: Time-Course of Effect *Davinia E. Withington, François Donati, David R. Bevan, and France Varin* 469

Additive Depressant Effects of Amiodarone Given With Halothane in Isolated Hearts *Rosemary T. Rooney, David F. Stowe, Jure Marijic, John P. Kampine, and Zeljko J. Bosnjak* 474

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 by the International Anesthesia Research Society. Second class postage paid at New York, NY and at additional mailing offices. Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year; in all other countries, $110.00. (See General Information in this issue for further details regarding membership.) Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico; $55.00 for surface airlift to Europe; $75.00 for surface airlift to Japan; and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: Anesthesia and Analgesia, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

NORMOTHERMIA IN THE O.R.

GUARANTEED*



BAIR HUGGER™
CONVECTIVE WARMING™
THERAPY STARTED

*Terms of guarantee:

1. Bair Hugger™ Convective Warming Therapy must begin immediately after induction of anesthesia on the "high" setting and continue throughout the case if indicated.

2. Infused blood and fluids must be warmed to body temperature.

If these two criteria are met and the patient is hypothermic at the end of the operation (core temperature <36°C), Augustine Medical will replace the Warming Cover. This guarantee is limited to the replacement of the Warming Cover.

Bair Hugger™

For more information about Bair Hugger™ Convective Warming Therapy, call 1-800-733-7775 or (612) 941-8866

AUGUSTINE MEDICAL INC.

PRACTICAL SOLUTIONS TO COMMON PROBLEMS IN ACUTE CARE™

10393 West 70th Street • Eden Prairie, Minnesota 5534

SCIENTIFIC ARTICLES—*continued*

Which Drug Prevents Tachycardia and Hypertension Associated With Tracheal Intubation: Lidocaine, Fentanyl, or Esmolol? *Steven M. Helfman, Martin I. Gold, Everard A. DeLisser, and Claire A. Herrington* 482

Computerized Continuous Infusion of Intravenous Anesthetic Drugs During Pediatric Cardiac Surgery *Frank H. Kern, Ross M. Ungerleider, James R. Jacobs, John L. Boyd III, J. G. Reves, David Goodman, and William J. Greeley* 487

Sequestration of Glyceryl Trinitrate (Nitroglycerin) by Cardiopulmonary Bypass Oxygenators *Brian P. Booth, Mark Henderson, Brian Milne, Frank Cervenko, Gerald S. Marks, James F. Brien, and Kanji Nakatsu* 493

One Hundred Percent Incidence of Hemidiaphragmatic Paresis Associated With Interscalene Brachial Plexus Anesthesia as Diagnosed by Ultrasonography *William F. Urmey, Karl H. Talts, and Nigel E. Sharrock* 498

Postoperative Neuromuscular Function in Pediatric Day-Care Patients *Michael R. N. Baxter, Joan C. Bevan, Jacob Samuel, François Donati, and David R. Bevan* 504

Sensory and Motor Blockade During Epidural Analgesia With 1%, 0.75%, and 0.5% Ropivacaine—A Double-Blind Study *Dusanka Zaric, Kjell Axelsson, Per-Anders Nydahl, Lennart Philipsson, Pål Larsson, and Jan Robert Jansson* 509

Continuous Infusion of Interpleural Bupivacaine Maintains Effective Analgesia After Cholecystectomy *Charles E. Laurito, Louise I. Kirz, Timothy R. VadeBoncouer, Francis X. Riegler, Gregg M. Citron, Laurence J. Segil, and Dale A. Pelligrino* 516

Comparison of Epidurally Administered Sufentanil, Morphine, and Sufentanil-Morphine Combination for Postoperative Analgesia *Raymond S. Sinatra, Ferne B. Sevarino, James H. Chung, George Graf, Darcy Paige, Victor Takla, and David G. Silverman* 522

Effects of Clear Liquids on Gastric Volume and pH in Healthy Volunteers *Ketan Shevde and Narendra Trivedi* 528

Effects of H_2-Receptor Blockers on Response of Cerebral Blood Flow to Normocapnic Hypoxia *G. Audibert, C. Saunier, D. Hartemann, O. Bigard, and J. P. Haberer* 532

HISTORICAL ARTICLE

The Development of Academic Anesthesiology at the Roswell Park Memorial Institute: James O. Elam, MD, and Elwyn S. Brown, MD *James E. Peppriell, Douglas R. Bacon, Mark J. Lema, Richard Ament, and Clifton K. Yearley* 538

CLINICAL REPORTS

Plasma Concentration of Bupivacaine After Stellate Ganglion Blockade *Hinnerk Wulf, Christoph Maier, Hans-Albrecht Schele, and Wolfgang Wabbel* 546

Respiratory Failure Associated With Amnioinfusion During Labor *Debbie A. Dragich, Alan F. Ross, David H. Chestnut, and Katharine Wenstrom* 549

Stellate Ganglion Blocks in Pediatric Patients *Winston C. V. Parris, Bhaskar C. Reddy, Houston W. White, and David M. McGrath* 552

CLINICAL REPORTS—*continued*

Acute Dystonia After Alfentanil in Untreated Parkinson's Disease *Berend Mets* 557

Venous Air Embolism Occurring After Removal of a Central Venous Catheter *W. Sherman Turnage and James V. Harper* 559

LETTERS TO THE EDITOR

Is Observing the Patient a Thing of the Past? *Gerald Edelist* 561

In Response *Mitchel B. Sosis* 561

A Case for the Removal of the Retained Intrathecal Catheter *Carol A. Pasquariello and Randal R. Betz* 562

Blood Pressure Values in Parturients: Auscultatory Versus Oscillatory Values *Gertie F. Marx, David R. Sofair, and Scott I. Winikoff* 562

A Simple Device to Monitor Neuromuscular Blockade *E. Alan Moretti, Ronald Cardoso, Mehrdad Rafizadeh, and Robert Ciolino* 563

Just the Fax, Ma'am *Francis X. Dillon, Nancy Zinni, and Mary Glass* 564

A Safer Continuous Lumbar Plexus Block Technique? *George W. Rung* 564

Single-Bolus Injection of Esmolol for Treatment of Intraoperative Tachycardia *Steven R. Ford* 565

Insulated Circuit Hose Improves Heated Humidifier Performance in Anesthesia Ventilation Circuits *Alan R. Mizutani, George Ozaki, and Ronald Rusk* 566

Leakage of Anesthetic Agent From an Ohmeda Tech IV Vaporizer *Donald B. Goldman and Phillip S. Mushlin* 567

BOOK REVIEWS

Treatment of Chronic Pain: Possibilities, Limitations and Long-Term Follow-up by M. Mumenthaler, P. A. Van Zwieten, and J. M. Farcot, eds. *Steven D. Waldman* 568

Clinical Neuroanesthesia by R. F. Cucchiara and J. D. Michenfelder, eds. *David S. Smith* 568

Hemorrhagic Disorders by Bruce D. Spiess, ed. *Carter P. Dodge* 569

The ICU Book by Paul L. Marino *Thomas L. Higgins* 570

Books Received 570

A Guide for Authors A39

Anesthesia
and Analgesia

Journal of the International Anesthesia Research Society

General Information

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, Edward D. Miller, Jr, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, Stephen J. Thomas, MD, John L. Waller, MD, and K. C. Wong, MD, PhD. Emeritus Trustees are: Paul R. Dumke, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Morris J. Nicholson, MD, B. B. Sankey, MD, and T. H. Seldon, MD.

Anesthesia and Analgesia (ISSN 0003-2999) is issued monthly for the IARS in two indexed volumes per year by Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Printed in USA. © 1991 by the International Anesthesia Research Society. Second class postage paid at New York, NY and at additional mailing offices.

Subscription information for 1991 applying to IARS members: USA and possessions, $90.00 per year; in all other countries, $110.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. Associate Membership is available to individuals certified, licensed, or accredited by anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). Educational Membership (half the full-member price) is available to interns, residents, and students in nurse anesthesia and related training programs, for a 2-, 3-, or 4-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: International Anesthesia Research Society, Suite 140, 2 Summit Park Drive, Cleveland, OH 44131-2553.

Subscription information for 1991 applying to non-IARS members: Institutions, $140.00; nonmember individuals, $100.00. Outside the USA and possessions, please add $20.00 for surface postage and handling. For airmail, add $75.00 in USA, Canada, and Mexico; $55.00 for surface airlift to Europe; $75.00 for surface airlift to Japan; and $145.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

Single issues: Single copy information is available from Elsevier Science Publishing Co., Inc., upon request. Back volume (all issues prior to 1983) information is available from the IARS.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc., 440 Park Avenue South, 14th Floor, New York, NY 10016. Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claim made of it by its manufacturer.

No responsibility is assumed by the Publisher for any injury and/or damage to persons or property as a matter of products liability, negligence, or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein. No suggested test or procedure should be carried out unless, in the reader's judgment, its risk is justified. Because of rapid advances in the medical sciences, we recommend that the independent verification of diagnoses and drug dosages should be made. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors.

See Classified Ads section for submission of classified ad material.

All articles published in this journal become the property of the International Anesthesia Research Society. This journal has been registered with the Copyright Clearance Center, Inc. Consent is given for the copying of articles for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition that the copier pay through the center the per copy fee stated in the code on the first page of each article for copying beyond that permitted by the US Copyright Law. If no code appears on an article, the author has not given broad consent to copy, and permission to copy must be obtained directly from the author. This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising and promotional purposes, or for creating new collective works.

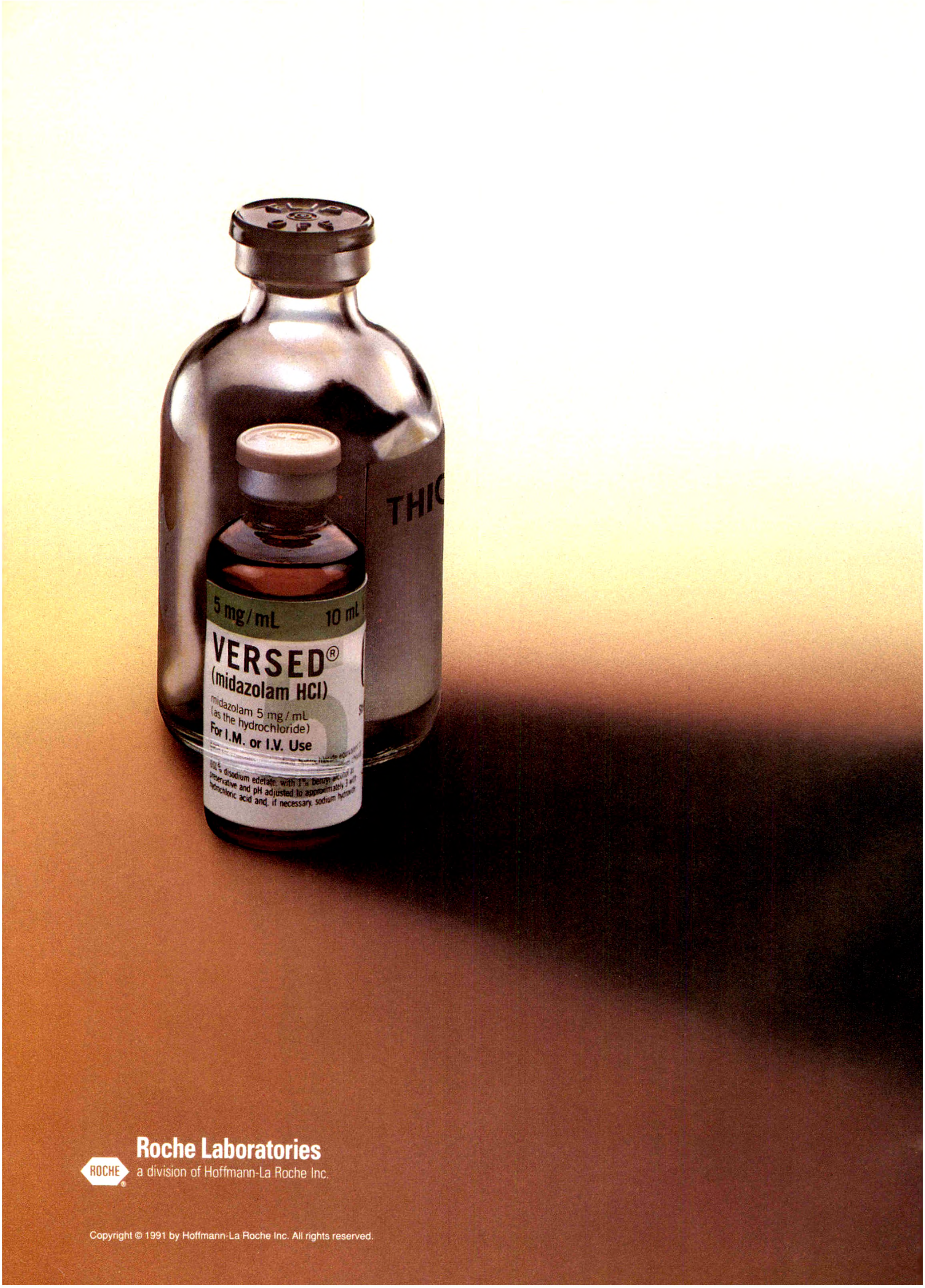
All inquiries regarding copyrighted material from this publication, other than reproduction through the Copyright Clearance Center, should be directed to: Rights and Permissions Department, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. FAX 212-633-3977.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) are processed through Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010. Prices are provided upon request.

This journal is abstracted/indexed in: Biological Abstracts, Chemical Abstracts, Current Contents/Life Sciences, Current Contents/Clinical Practice, Excerpta Medica, Index Medicus, ISI/Biomed, and Science Citation Index.

On line text is available through BRS Colleague, 8000 Westpark Drive, McLean, VA 22102. Telephone: (800) 289-4277.

This journal is printed on acid-free paper.



Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED_{50} of barbiturates or narcotics up to 75%.[1-4] This synergistic effect appears to result from a mutual enhancement of binding-site affinity.[1-3] Clinically, co-induction may decrease toxicity and speed recovery.[2] VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,[5] and its potent amnestic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- **Allows lower doses of induction agents[1-5]**
- **A smooth induction[5,6]**
- **Less risk of breakthrough awareness[5,6]**
- **A smooth emergence[5,6]**

Dosing considerations

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE

VERSED®

midazolam HCl/Roche ⒸⅣ

FIRST

Injectable VERSED is available in 1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, *et al*. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg*. 1988;67:342-345. **2.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology*. 1990; 73(3A):A1216. **3.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69:213-217. **4.** Ben-Shlomo I, *et al*. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth*. 1990;64:45-47. **5.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology*. 1982;57:279-284. **6.** Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiol Scand*. 1990;34(suppl 92):48-50.

VERSED®
(brand of midazolam HCl/Roche) Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED.

Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes coma, untoward effects on vital signs). No specific organ toxicity would be expected.

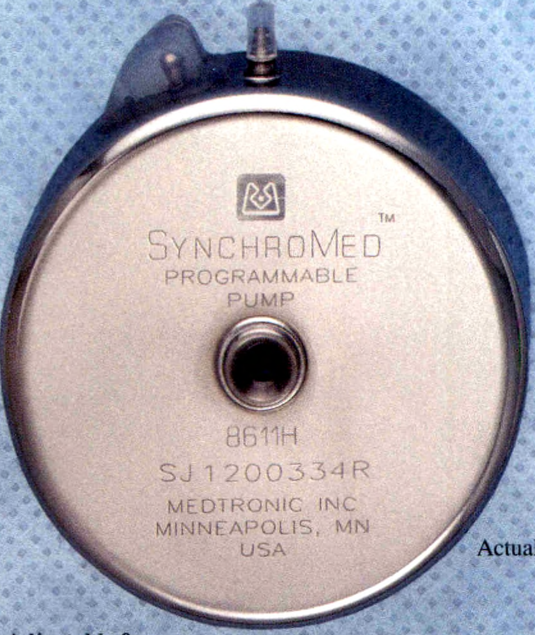
DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

Roche Laboratories
a division of Hoffmann-La Roche Inc.

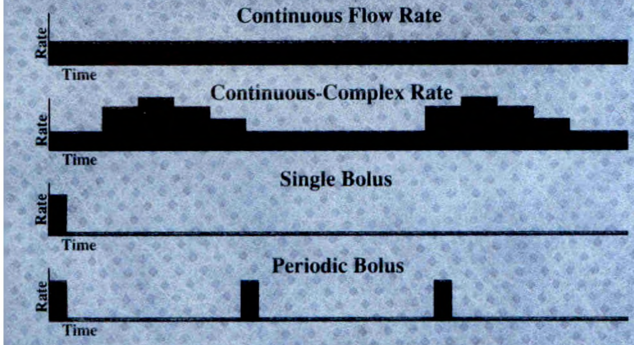
340 Kingsland Street
Nutley, New Jersey 07110-1199

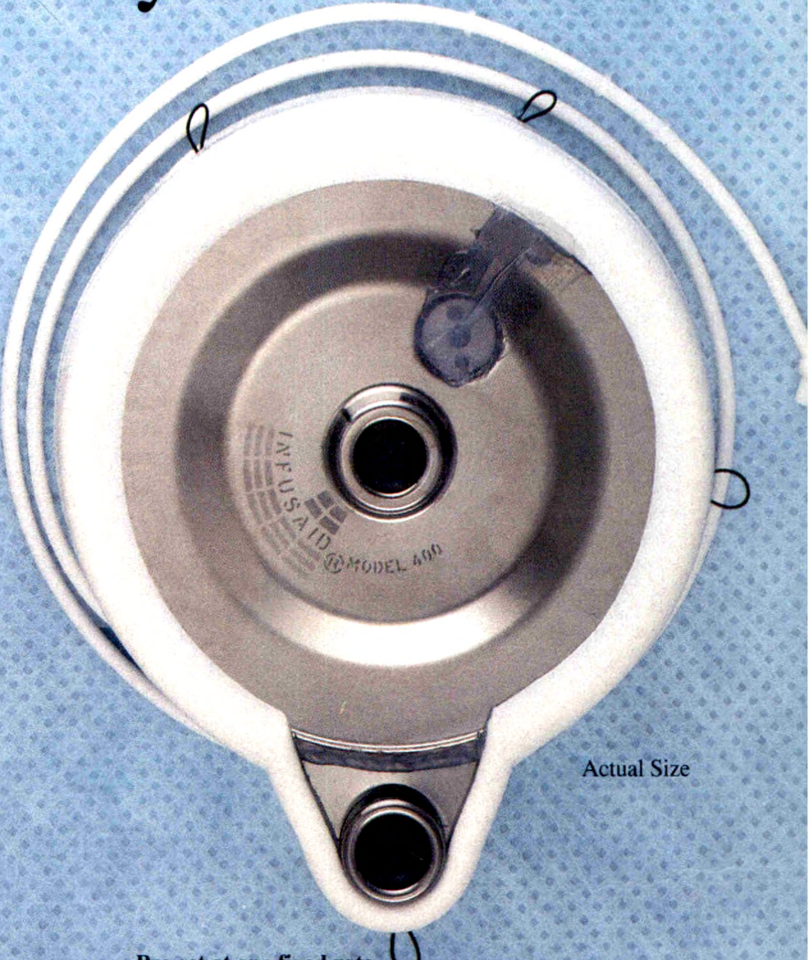
Only one implantable is smart enough to follow all of your orders.



Actual Size

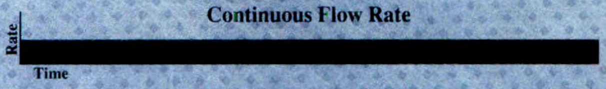
Adjustable from 0.1 to 18 ml/day...





Actual Size

Pre-set at one fixed rate...



SynchroMed® Programmable Pump does exactly what you want it to do.

Non-programmable alternative does only what it was built to do.

With the SynchroMed Programmable Pump, **flow rate is easily programmed** for whatever variable or continuous infusion schedule you think is best. Accuracy is unaffected by the environment. And, as patient requirements change, flow rate adjustment is non-invasive for comfort and safety.

More than just follow orders, the pump can tell you the patient's I.D., drug type, concentration, remaining volume, flow rate and date last programmed.

This combination of flexibility, precision and responsiveness is impossible with the non-programmable unit which operates only at the rate built in by the manufacturer.

The SynchroMed Pump is also smaller and almost 50 g lighter when filled. Yet, it **requires fewer refills.** With computer-based technology engineered into the compact device, flow rates can be lower, and refill periods longer. For refills, you can readily **use pre-mixed concentrations** and save time in the pharmacy.

If you'd like to further evaluate the benefits of the only implantable programmable pump commercially available, contact us for more information and free educational materials.

Medtronic

Medtronic Neurological Division 800 53rd Avenue N.E. Minneapolis, MN 55421 Attn: N340-DH 800-328-0810 / 612-572-5000

Copyright © 1991 by Medtronic, Inc., Minneapolis, Minnesota USA

NP-1304 UC9003081EN

SYNCHROMED®
INFUSION SYSTEM

The Implantable Pump with External Control

Indications

The SynchroMed Infusion System is indicated for use when patient therapy requires the chronic intravascular infusion of floxuridine or doxorubicin. In addition, the nontherapeutic use of bacteriostatic water, physiological saline, and/or heparin is indicated necessary to support this mode of cancer therapy.

The regional intra-arterial infusion of floxuridine is used in the palliative management of unresectable solid colorectal tumors metastatic to the liver.

The systemic intravenous infusion of doxuribicin is used in the palliative management of various solid tumors, lymphomas, and leukemias.

Bacteriostatic water or physiological saline can be used to achieve the physician-prescribed concentration of floxuridine or doxorubicin or to flush the pump reservoir. Heparinized physiological saline may be used during an interruption in floxuridine therapy to maintain catheter patency.

Physicians prescribing the SynchroMed Infusion System for use with floxuridine or doxorubicin sterile solution must be familiar with the indications, contraindications, and warnings described in the drug labeling. Except under approved conditions of Investigational Device Exemptions, the use of the SynchroMed Infusion System is restricted to the infusion of the drugs and fluids previously described.

Contraindications

The device should not be implanted in the presence of infection.

Implantation is contraindicated when the pump cannot be implanted less than 2.5 cm (one inch) from the surface of the skin and/or when the patient has an implanted programmable medical device.

Patients whose body size is not sufficient to accept the pump bulk and weight are not suitable.

Contraindications relating to the use of the prescribed drug should be observed.

Copyright 1991 Medtronic, Inc.
NP-1304 UC9003081EN
All rights reserved.

United States of America
Medtronic Neurological
800 53rd Avenue, N.E.
Minneapolis, MN 55421
Telephone: (612) 572-5000
FAX: (612) 572-5078
Toll-Free: 1-800-328-0810

Europe
Medtronic Europe
25 rue Chateaubriand
75008 Paris, France
Telephone: (33-1) 42-56-46-88
Telex: 643-449
FAX: (33-1) 42-56-07-66

Canada, Latin America
Medtronic of Canada, Ltd.
6733 Kitimat Road
Mississauga, Ontario L5N 1W3
Canada
Telephone: (416) 826-6020
FAX: (416) 826-6620
Toll-free: 1-800-268-5346

Asia-Pacific
Medtronic Asia-Pacific
Shuwa Kioi-cho Park
Building, 5F
3-6 Kioi-cho, Chiyoda-ku
Tokyo 102, Japan
Telephone: (03) 230-2919
Telex: J23920 HYMEDTRO
FAX: (03) 230-0446

IARS REVIEW COURSE LECTURES AVAILABLE

____ 1991, 65th Congress—26 Review Course Lectures—$10.00

____ 1990, 64th Congress—26 Review Course Lectures—$10.00

____ 1989, 63rd Congress—27 Review Course Lectures—$10.00

____ 1988, 62nd Congress—26 Review Course Lectures—$10.00

____ 1987, 61st Congress—25 Review Course Lectures—$6.00

____ 1986, 60th Congress—26 Review Course Lectures—$6.00

____ 1985, 59th Congress—26 Review Course Lectures—$6.00

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

Please send Lecture Booklets checked above.

My check payable to IARS in the amount of $________ is enclosed.

____
(Name)

____
(Mail Address)

____

____
(City, State, Zip)

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

IARS 66TH CONGRESS

Friday, March 13 through Tuesday, March 17, 1992
Hilton & Towers, San Francisco, California

CALL FOR PAPERS

AUGUST 2, 1991, DEADLINE

The Program Committee for the IARS 66th Congress cordially invites submission of abstracts for consideration as oral or poster presentations at the 1992 meeting in San Francisco. The official abstract application and transmittal forms are available from the Cleveland office of the IARS:

International Anesthesia Research Society
2 Summit Park Drive, Suite 140
Cleveland, OH 44131, USA
Telephone: (216) 642-1124

Please note the absolute deadline for receipt of completed applications is August 2, 1991. Please request forms promptly—either by calling the telephone number above or returning the form below.

- -

International Anesthesia Research Society
2 Summit Park Drive, Suite 140
Cleveland, OH 44131

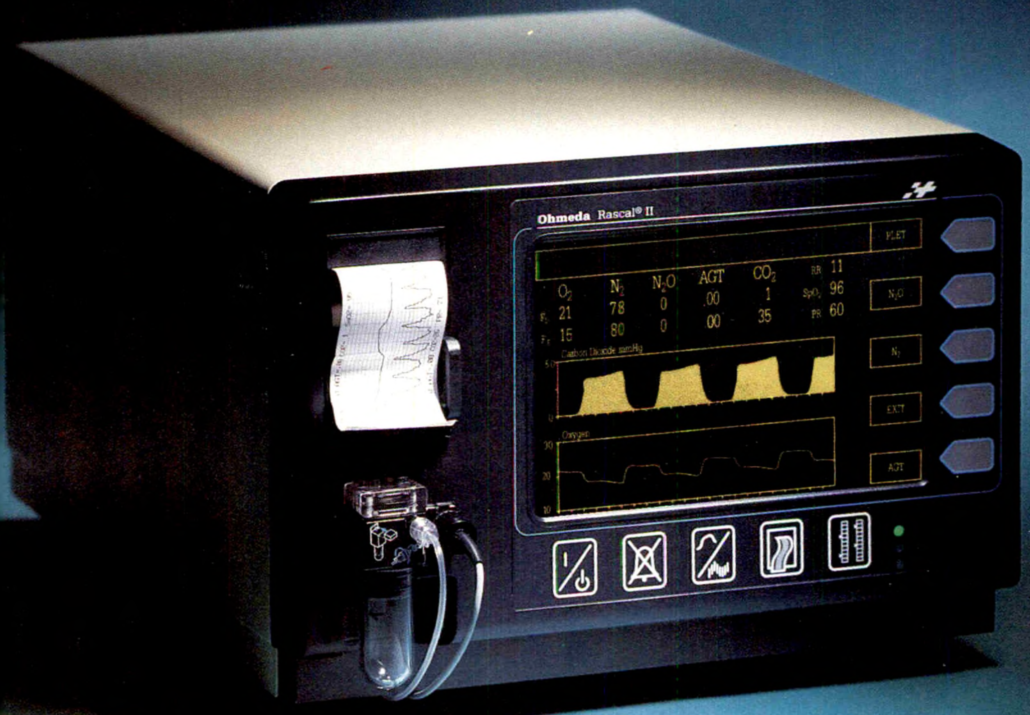
Please send ______ abstract submission packet(s) for the IARS 66th Congress to:

Name: ____

Mail Address: ______________________________________

____

Introducing Rascal® II. Total gas analysis in a whole new light.



ou've waited long enough for a edicated respiratory gas moni-oring system that identifies all nesthetic agents and measures nspired and expired O_2 as well s nitrogen. A system with the ccuracy and completeness of ass spectrometry, but dedi-ated to your patient alone.

A system like the new Rascal II from Ohmeda.

The Rascal II uses patented Laser-Raman™ light scattering technology to perform gas analysis. The result is the first truly comprehensive respiratory gas monitor that can fit right on your anesthesia machine.

With Rascal II from Ohmeda, total gas analysis means greater protection for your patient. And greater peace of mind for you.

To learn more about Rascal II, contact us today. We think you'll agree. The Rascal II puts respiratory gas monitoring in a whole new light.

Ohmeda

Editorials

Ethics in Publishing

Graham Smith, BSc, MD, FCAnaes, Editor, *British Journal of Anaesthesia,* Ronald D. Miller, MD, Editor-in-Chief, *Anesthesia and Analgesia,* Lawrence J. Saidman, MD, Editor-in-Chief, *Anesthesiology,* and M. Morgan, FCAnaes, Editor, *Anaesthesia*

Editors from some major biomedical journals published in English met in Vancouver, British Columbia, and drew up technical requirements for manuscripts to be submitted to these journals. The Vancouver group evolved into the International Committee of Medical Journal Editors, which in 1981 revised the requirements and published a second edition in 1982 and a third edition in 1988 (1). Although the *Uniform Requirements* describe mainly the way in which a manuscript should be prepared, they also make important recommendations on some ethical aspects: notably prior and duplicate publication, authorship, financial relationships posing conflict of interests, and requirements that procedures were conducted in accordance with the ethical standards of the appropriate committee on human experimentation or with the Helsinki Declaration.

More specifically with respect to duplicate publication, in the *Uniform Requirements* it is stated that most journals do not wish to consider for publication a paper describing work that has already been reported elsewhere or that has been submitted or accepted for publication elsewhere. (This does not preclude considering a paper that has been rejected by another journal or a complete report of a preliminary communication.) When submitting a paper, an author should always make a full statement about all submissions and previous reports that might be regarded as prior or duplicate publication of the same or very similar work, and copies of such material should be included with the submitted paper.

As the *Uniform Requirements* are not immediately available to most authors, many journals including *Anesthesiology, Anesthesia and Analgesia, Anaesthesia,* and the *British Journal of Anaesthesia* publish an individual guide to contributors that summarizes these findings and describes specific requirements. In our Guide for Authors, it is stated clearly that papers submitted must not have been submitted to or published *in whole* or *in part* in any other journal. Despite these well-publicized strictures, there have been several examples in the past 2 years wherein material published in or submitted to one of our journals has been either simultaneously submitted to or published in a second anesthesia journal.

An example of duplicate publication that authors may think acceptable but that we invariably reject, comprises the use of control data to compare with one situation in one journal and the same control data to compare against a second circumstance in a paper submitted to another journal. When authors fail to indicate in their list of references that material is "in press" or published recently in another journal, one conclusion is that the authors are deliberately practicing deception.

For the past 8 years, an International Meeting of Editors of Anaesthetic Journals has convened at 2-year intervals coinciding with either a European or World Congress of Anesthesiology. At the most recent Fourth Meeting held in association with the Eighth European Congress of Anaesthesiology in Warsaw in 1990, there was some discussion of ethical problems in publishing. The most common and obvious problem discussed was that of duplicate submission and publication. This may be classified broadly into two types:

1. Reproduction in one journal of data identical to those published elsewhere with either similar or differing discussions. This is clearly unacceptable and represents a breach of copyright. Authors should be aware of the fact that reproduction of

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

blocks of text, tables, or figures always necessitates permission of both authors and editors.

2. The use of identical control data in two different papers, as noted above.

An additional issue of concern is the submission of various aspects of one single study to several different journals. Although this does not represent multiple publication per se, it nonetheless represents publication of an unnecessary number of papers and detracts from the interpretation of single manuscripts. All the editors present at the Fourth International Meeting of Editors of Anaesthetic Journals in Warsaw in 1990 were opposed to this type of practice and would request that all data from a single circumscribed study be submitted to one journal.

This international collaboration is illustrated by the fact that this joint editorial is appearing simultaneously in *Anesthesiology, Anesthesia and Analgesia*, the *British Journal of Anaesthesia*, and *Anaesthesia*. The views expressed on duplicate publication are also supported fully by David Bevan who is publishing a similar editorial in this month's issue of the *Canadian Journal of Anaesthesia* and also by John Roberts who will be referencing this article in an editorial in *Anaesthesia and Intensive Care*.

Improving communication between the editors of biomedical journals should facilitate detection of any failure of authors to follow the recommendations of the International Committee of Medical Journal Editors, and we hope that authors become aware of and exercise their responsibilities related to submission of manuscripts. Research published in biomedical journals must be held to the highest standards, and adherence to ethical standards in publishing is an absolute expectation of our readers as well as the public.

References

1. International Committee for Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Br Med J 1988;296:401–5.

Glucose Management During Cardiopulmonary Bypass: Cardiovascular and Neurologic Implications

William L. Lanier, MD

Key Words: ANESTHESIA, CARDIOVASCULAR—cerebral function and blood glucose levels. BRAIN, CEREBRAL FUNCTION AND BLOOD GLUCOSE—ischemia.

Metz and Keats (1) report in the present issue on the relationship between glucose-containing priming solutions in the cardiopulmonary bypass (CPB) circuit and perioperative cardiac and neurologic function. Their conclusions are twofold: first, glucose solutions in the CPB circuit reduce intraoperative fluid requirements and improve perioperative fluid balance; and, second, glucose does not increase postoperative neurologic injury.

When reduced to its essence, the study by Metz and Keats had a single positive finding: glucose-treated subjects had a more favorable perioperative fluid balance. The use of glucose was associated with increased urine output, but it did not alter inotrope use, diuretic requirement, or hospital course. The greatest difference in fluid requirement occurred during the CPB period: glucose-treated subjects received one-eighth the amount of crystalloid given to non-glucose-treated patients (144 ± 270 vs 1147 ± 1149 mL; mean ± SD; $P < 0.001$). The decision to give fluid during CPB was based on the status of the CPB-reservoir volume, and flexibility was permitted "depending on (the) stage of operation." The process was not blinded.

The second conclusion of the study by Metz and Keats was that glucose administration during CPB and coronary artery bypass grafting (CABG) does not adversely affect postoperative neurologic function. This conclusion, based on data from their study and from their interpretation of the related literature, deserves comment.

The study by Metz and Keats evaluated 107 patients undergoing CABG. They reported only two instances of neurologic injury in these patients (i.e., an incidence of 2%). Although Metz and Keats did not describe how neurologic injury was assessed, both recorded episodes of neurologic dysfunction were grossly evident. Neither instance of neurologic dysfunction occurred in the group that received glucose; thus, the authors concluded that glucose, per se, imposed no detrimental neurologic effect. Their approach to this issue and their conclusions are perplexing. In a previous report from the same institution, Slogoff, Girgis, and Keats demonstrated that the incidence of transient and persistent neurologic abnormalities after CABG was 6% and 3%, respectively (2). These numbers were matched by a similar incidence of transient and persistent psychiatric alterations in CABG patients (9% and 3%, respectively), assessed by sophisticated testing procedures. When both neurologic and psychiatric alterations were assessed, the incidence in CABG patients was approximately one-half that found in patients having open ventricle procedures. Thus, by using CABG patients in the present study and presumably by using less rigorous neurologic and psychiatric assessment than had previously been reported from their institution (2), Metz and Keats (1) appear to have biased their study toward a negative result. In striking contrast, Nussmeier, Arlund, and Slogoff—again at the same institution—used the higher risk group of patients (i.e., patients having open ventricle procedures) and the combination of rigorous neurologic and psychiatric evaluation to assess the effect of thiopental loading on post-CPB neurologic function (3). In the latter study, 182 patients were included, and the thiopental group experienced a zero incidence of persistent neuropsychiatric injury compared to an 8% incidence in the control group. Despite these rigorous study conditions and the large number of subjects, statistical significance barely exceeded the accepted minimal criteria (i.e., P was <0.025). Based on these data, it would appear that in patients having CPB, less rigorous study conditions (i.e., a smaller number of patients, CABG patients rather than open ventricle

---

Received from the Department of Anesthesiology, Mayo Clinic and Mayo Medical School, Rochester, Minnesota. Accepted for publication November 17, 1990.

Address correspondence to Dr. Lanier, Department of Anesthesiology, Mayo Clinic, 200 First Street, S.W., Rochester, MN 55905.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

patients, and apparently less rigorous neurologic and psychiatric assessment) almost guarantee a negative outcome in attempting to assess the impact of any specific intervention. Furthermore, Metz and Keats (1) may also have biased their study by excluding patients over 75 yr of age because this "characteristic predispose[s] to central nervous system deficits after CPB," even though previous studies in the same institution included "any adult patient" (3).

When arguing for the safety of using glucose-containing CPB priming solutions, Metz and Keats point out that there are no studies demonstrating worse neurologic outcome when glucose treatment is given to patients undergoing cardiac operations. Regarding this point, the authors are certainly correct; in humans, the evidence remains anecdotal only. There is inadequate prospective evidence in the literature suggesting an association between glucose and neurologic outcome in humans, regardless of the setting. Steward et al. (4), in a letter, suggested a worse neurologic outcome in children with elevated blood glucose during profound hypothermia and circulatory arrest for intracardiac surgery; however, the study was retrospective, the sample size was small (n = 34), and statistical significance was not achieved. The dearth of published data addressing the specific situation addressed by Metz and Keats is probably related to the fact that prospective randomized studies using blinded observers of neurologic function are just recently gaining momentum in the literature. The energy and discipline demanded of teams of individuals who perform this type of investigation are awe-inspiring and deserve our greatest support and respect. However, the absence of such studies for a given therapy should not be misinterpreted as evidence for an absence of effect of the therapy.

Metz and Keats next argue that the type of ischemia that occurs after CPB results from a pathologic mechanism that makes it difficult to extrapolate from existing experimental studies to the situation of post-CPB injury. Their review of the literature is used to support their position. This same body of literature can be used to refute their position.

Neurologic injury after CPB is likely due to (a) focal ischemia (e.g., resulting from emboli) or (b) either incomplete or complete global cerebral ischemia (e.g., resulting from either low flows or circulatory arrest, respectively). In these circumstances, there is evidence in the literature of an association between glucose administration and/or hyperglycemia and increased postischemic neurologic injury. The proposed mechanism by which glucose exacerbates postischemic neurologic injury is as follows. The anaerobic metabolism of glucose during ischemia results in an intracellular lactic acidosis (5). This acidosis, in turn, initiates or facilitates a cascade of secondary processes that result in permanent neurologic injury (6). Based on the proposed mechanism, one might anticipate a similar effect of glucose on outcome after both global and focal ischemia.

There is consistent evidence of glucose-induced enhancement of injury in studies of global cerebral ischemia (7–13), and the majority of studies in focal cerebral ischemia also suggest that glucose worsens outcome (14–29). However, in three studies of focal cerebral ischemia, there is evidence of improved outcome following glucose treatment (19,27,28). This has led some investigators (27,28) to speculate that in settings in which cerebral blood flow reduction is less than complete (i.e., as may occur in the penumbra of focally ischemic brain), glucose may have a beneficial effect similar to that observed in neurons studied during anoxia in vitro (30). According to this logic, both in studies of incomplete ischemia and in studies performed in vitro, the potential for accumulation of toxic metabolites is reduced during periods of decreased oxygen delivery. In the absence of accumulation of these metabolites, glucose may have a direct beneficial effect on anoxic or hypoxic neurons. Although the in vitro data (30) and some in vivo data (20) support this hypothesis, other in vivo data directly discount the hypothesis (8). Nedergaard and Diemer (20) studied the effect of glucose on postischemic histology in a diabetic rat model of middle cerebral artery occlusion. They found that glucose resulted in less severe histologic damage in the cortical infarct rim (i.e., the penumbral area). However, this apparent benefit to cortical rim neurons occurred at the expense of more severe histologic damage in the core of the ischemic area, and—depending on the duration of the hyperglycemic, diabetic state—either no change or an increase in infarct volume. In contrast to this evidence of possible selective neuronal benefit of glucose in low flow areas in a middle cerebral artery occlusion model (20) are data from the four-vessel occlusion model in rats reported by Pulsinelli et al. (8). The four-vessel occlusion model produces near-complete forebrain ischemia and incomplete hindbrain ischemia (5). In both brain areas, glucose produced more severe histologic injury. Taken together, these and other studies (8,14–30) suggest that during incomplete ischemia, any potentially beneficial effect of glucose in small populations of isolated neurons may be offset by an adverse effect in larger populations of ischemic neurons. Thus, during incomplete ischemia, the net effect on the brain of increased glucose concentrations will likely

Table 1. Glucose and Neurologic Outcome After Global Cerebral Ischemia

Authors	Reference	Species	Glucose effect
Myers and Yamaguchi	7	Monkeys	Worse function and histology[a]
Pulsinelli et al.	8	Rats	Worse histology
Longstreth et al.	9	Humans	Worse function
Longstreth and Inui	10	Humans	Worse function
D'Alecy et al.	11	Dogs	Worse function
Lanier et al.	12	Monkeys	Worse function and histology
Nakakimura et al.	13	Cats	Worse function[b]

[a] This study contained the first report of glucose-induced enhancement of ischemic neurologic injury. The number of subjects was insufficient for statistical comparisons.

[b] There was a tendency toward more severe histologic injury in glucose-treated subjects ($P = 0.07$) in this study.

Table 2. Glucose and Neurologic Outcome After Focal Cerebral Ischemia

Authors	Reference	Species	Glucose effect
Pulsinelli et al.	14	Humans	Worse function
Brint et al.	15	Rats	Worse infarct size
Candelise et al.	16	Humans	Worse function and lesion size[a]
Berger and Hakim	17	Humans	Worse function and CT observations
Cox and Lorains	18	Humans	No effect on function
Ginsberg et al.	19	Rats	Improved infarct size
Nedergaard and Diemer	20	Rats	Worse histology; worse or no change in infarct size
Nedergaard	21	Rats	Worse infarct size[b]
Woo et al.	22	Humans	Worse function
Adams et al.	23	Humans	No effect on function or CT lesion size[c]
De Courten-Myers et al.	24	Cats	Worse infarct size
Prado et al.	25	Rats[d]	Worse cortical infarct size
Prado et al.	25	Rats[d]	No effect on cortical infarct size
Kiers et al.	26	Humans	Worse function and infarct size[a]
Zasslow et al.	27	Cats	Improved size of injury[e]
Kraft et al.	28	Rabbits	Improved size of injury[e]
Hoffman et al.	29	Rats[f]	Worse function

CT, computed tomography.

[a] Ischemic lesion size was determined using computed tomography scans.

[b] Histology was described as more abnormal in glucose-treated rats, but data were not subjected to statistical analysis.

[c] All patients received high-dose naloxone therapy.

[d] This study reported on two models of focal cerebral ischemia having differing severity of cortical ischemia.

[e] Using a histologic assessment of size of injury.

[f] This model is primarily of focal cerebral ischemia; however, it also includes an incomplete global ischemia component.

be one of detriment (i.e., an effect that is identical to that observed in the brain exposed to complete ischemia).

Metz and Keats also suggest that a period of reperfusion after ischemia may play a critical role in whether glucose has a beneficial or detrimental effect on postischemic injury. This hypothesis does not accommodate the fact that de Courten-Myers et al. (24) and Zasslow et al. (27) used the same model of focal ischemia in cats and neither provided a reperfusion period after ischemia. In one study (24), glucose resulted in worsened outcome; in the other (27), glucose resulted in an apparently beneficial outcome. As addressed below, the apparently beneficial effects of glucose in the Zasslow et al. study (27) and in some other studies of focal ischemia are probably not related to the presence or absence of a reperfusion state, nor do they represent evidence of isolated neuronal protection in low flow states. Instead, they may be due to factors other than those resulting in a long-term beneficial effect on neurons.

In the accompanying tables, I have summarized the literature regarding the association between glucose and global cerebral ischemia (Table 1) and glucose and focal cerebral ischemia (Table 2). In both, I have presented the available studies that examine either neurologic function or histology (i.e., the two markers of injury that are most relevant clinically). I have not discriminated between studies in which a cause-effect relationship between glucose and outcome was demonstrated versus studies in which there was an association but of undetermined origin. However, I have excluded studies that demonstrated a worse outcome from stroke in diabetics, but failed to document blood glucose values.

In seven of seven cited studies of glucose and global cerebral ischemia (7–13), increased glucose in the blood or brain was associated with a worse postischemic outcome (Table 1). In 11 of 17 cited studies of focal cerebral ischemia (14–29), there also was an association between glucose and worse postischemic outcome (Table 2). In the six studies of focal cerebral ischemia that did not identify this association, two studies in humans (18,23) found no relationship between glucose and neurologic injury (a conclusion that differed from five other similarly designed human studies [14,16,17,22,26]). The results of one human study (23) were confounded by high-dose naloxone therapy in all subjects. In three animal studies of focal cerebral ischemia, glucose produced an apparently beneficial effect. Of these three animal studies, one used a rat model of photochemical cortical thrombosis (19) in which brain injury is produced by a novel mechanism that has been criticized for potentially lacking relevance to human cerebrovascular disease (31). The model was subsequently modified in a manner that improved its relevance to human disease (i.e., thrombosis originated in feeding vessels, not end vessels) (25). After modification of the model, glucose either increased or had no effect on cortical infarct volume, depending on whether the model modification resulted in severe or mild cortical ischemia, respectively.

The remaining two animal studies that reported a beneficial effect of glucose on outcome after focal cerebral ischemia (i.e., the cat study of Zasslow et al. [27] and the rabbit study of Kraft et al. [28]) did not control for osmotic effects, they used a histologic marker of cell injury, and both discontinued the study immediately after the ischemic period (after only 6 h of ischemia) (27,28). Using a model that was anatomically and physiologically similar to the Zasslow et al. cat model (27), and physiologically similar to the Kraft et al. rabbit model (28), Little demonstrated in cats that an osmotic effect alone (i.e., such as that produced by intravenous mannitol) improved histologic findings (32). Thus it is possible that the immediate, apparently beneficial effects of glucose in the studies by Zasslow et al. (27) and Kraft et al. (28) were not representative of the possible long-term, injury-enhancing effects of glucose. This issue was perhaps resolved by another study performed by de Courten-Myers et al. (24). In that study (24), a cat model of permanent middle cerebral artery occlusion identical to that of Zasslow et al. was used, and the animals were allowed to recover for 2 wk. Thus neuronal injury was allowed sufficient time to mature (33), and the immediate beneficial effects of an osmotic load were bypassed. Under these circumstances, de Courten-Myers et al. (24) reported that glucose loading resulted in a worse ischemic injury. Hence, whether or not one discounts the studies having negative results or evidence of benefit from glucose, there remains a large body of convincing data that glucose worsens outcome from cerebral ischemia, including both global and focal ischemia, the types of ischemia most relevant to CPB patients.

Although Metz and Keats suggest that the risk of glucose-induced enhancement of ischemic neurologic injury is sufficiently small that it should not factor into our decision as to whether or not we should use a glucose-containing pump prime solution, the results of the present study are simply insufficient to draw such conclusions. Whether the beneficial effects of glucose on fluid balance outweigh the risk for glucose-induced enhancement of ischemic neurologic injury is not answered by this study. Until such proof appears—using prospective randomized studies with an appropriate number of subjects, blinded neurologic referees, and state-of-the-art neurologic and psychiatric evaluation—it is wise to manage glucose conservatively and use specific therapies (e.g., receptor-specific vasopressors and intravenous solutions that do not contain glucose) to alter cardiovascular function, vascular volume, and osmotic load. Although such a recommendation may seem excessively cautious, one must realize that neurologic and psychiatric dysfunction attributed to brain ischemia are reproducible phenomena after recovery from cardiac surgery and CPB. In the majority of reports in the literature, glucose administration and/or hyperglycemia worsened neurologic injury after cerebral ischemia. In contrast to these potentially detrimental effects of glucose in patients experiencing cardiac surgery and CPB, Metz and Keats reported a beneficial effect of glucose on perioperative fluid balance. However, the effects of glucose reported by Metz and Keats are apparently of temporary benefit only and do not appear to affect outcome.

References

1. Metz S, Keats AS. Benefit of a glucose-containing priming solution for cardiopulmonary bypass. Anesth Analg 1991;72: 428–34.
2. Slogoff S, Girgis KZ, Keats AS. Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. Anesth Analg 1982;61:903–11.
3. Nussmeier NA, Arlund C, Slogoff S. Neuropsychiatric complications after cardiopulmonary bypass: cerebral protection by a barbiturate. Anesthesiology 1986;64:165–70.
4. Steward DJ, Da Silva CA, Flegel T. Elevated blood glucose levels may increase the danger of neurological deficit following profoundly hypothermic cardiac arrest (letter). Anesthesiology 1988;68:653.
5. Plum F. What causes infarction in ischemic brain? The Robert Wartenberg Lecture. Neurology (NY) 1983;33:222–33.
6. Siesjo BK, Bengtsson F. Calcium fluxes, calcium antagonists, and calcium-related pathology in brain ischemia, hypoglycemia, and spreading depression: a unifying hypothesis. J Cereb Blood Flow Metab 1989;9:127–40.
7. Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. Arch Neurol 1977;34:65–74.
8. Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. Neurology (NY) 1982;32:1239–46.
9. Longstreth WT Jr, Diehr P, Inui TS. Prediction of awakening after out-of-hospital cardiac arrest. N Engl J Med 1983;308: 1378–82.
10. Longstreth WT Jr, Inui TS. High blood glucose level on hospital admission and poor neurologic recovery after cardiac arrest. Ann Neurol 1984;15:59–63.

11. D'Alecy LG, Lundy EF, Barton KJ, Zelenoch GB. Dextrose containing intravenous fluid impairs outcome and increases death after eight minutes of cardiac arrest and resuscitation in dogs. Surgery 1986;100:505–11.
12. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD. The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. Anesthesiology 1987;66:39–48.
13. Nakakimura K, Fleischer JE, Drummond JC, et al. Glucose administration before cardiac arrest worsens neurologic outcome in cats. Anesthesiology 1990;72:1005–11.
14. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 1983;74:540–4.
15. Brint S, Kraig R, Kiessling M, Pulsinelli W. Hyperglycemia augments infarct size in focal experimental brain ischemia (abstract). Ann Neurol 1985;18:127.
16. Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycemia in acute stroke. Arch Neurol 1985;42:661–3.
17. Berger L, Hakim A. The association of hyperglycemia with cerebral edema in stroke. Stroke 1986;17:865–71.
18. Cox NH, Lorains JW. The prognostic value of blood glucose and glycosylated haemoglobin estimation in patients with stroke. Postgrad Med J 1986;62:7–10.
19. Ginsberg MD, Prado R, Dietrich WD, Busto R, Watson BD. Hyperglycemia reduces the extent of cerebral infarction in rats. Stroke 1987;18:570–4.
20. Nedergaard M, Diemer NH. Focal ischemia of the rat brain, with special reference to the influence of plasma glucose concentration. Acta Neuropathol 1987;73:131–7.
21. Nedergaard M. Transient focal ischemia in hyperglycemic rats is associated with increased cerebral infarction. Brain Res 1987;408:79–85.
22. Woo E, Chan YW, Yu YL, Huang CY. Admission glucose level in relation to mortality and morbidity outcome in 252 stroke patients. Stroke 1988;19:185–91.
23. Adams HP Jr, Olinger CP, Marler JR, et al. Comparison of admission serum glucose concentration with neurologic outcome in acute cerebral infarction: a study in patients given naloxone. Stroke 1988;19:455–8.
24. De Courten-Myers G, Myers RE, Schoolfield L. Hyperglycemia enlarges infarct size in cerebrovascular occlusion in cats. Stroke 1988;19:623–30.
25. Prado R, Ginsberg MD, Dietrich WD, Watson BD, Busto R. Hyperglycemia increases infarct size in collaterally perfused but not end-arterial vascular territories. J Cereb Blood Flow Metab 1988;8:186–92.
26. Kiers L, Davis SM, Larkins RG, et al. Pathogenesis and outcome of stroke in diabetes and hyperglycemia (abstract). Stroke 1989;20:138.
27. Zasslow MA, Pearl RG, Shuer LM, Steinberg GK, Lieberson RE, Larson CP Jr. Hyperglycemia decreases acute neuronal ischemic changes after middle cerebral artery occlusion in cats. Stroke 1989;20:519–23.
28. Kraft SA, Larson CP Jr, Shuer LM, Steinberg GK, Benson GV, Pearl RG. Effect of hyperglycemia on neuronal changes in a rabbit model of focal cerebral ischemia. Stroke 1990;21:447–50.
29. Hoffman WE, Braucher E, Pelligrino DA, Thomas C, Albrecht RF, Miletich DJ. Brain lactate and neurologic outcome following incomplete ischemia in fasted, nonfasted, and glucose-loaded rats. Anesthesiology 1990;72:1045–50.
30. Schurr A, West CA, Reid KH, Tseng MT, Reiss SJ, Rigor BM. Increased glucose improves recovery of neuronal function after cerebral hypoxia in vitro. Brain Res 1987;421:135–9.
31. Helgason CM. Blood glucose and stroke. Stroke 1988;19:1049–53.
32. Little JR. Modification of acute focal ischemia by treatment with mannitol. Stroke 1978;9:4–9.
33. Pulsinelli WA, Brierly JB, Plum F. Temporal profile of neuronal damage in a model of transient forebrain ischemia. Ann Neurol 1982;11:491–8.

Benefits of a Glucose-Containing Priming Solution for Cardiopulmonary Bypass

Samuel Metz, MD, and Arthur S. Keats, MD

METZ S, KEATS AS. Benefits of a glucose-containing priming solution for cardiopulmonary bypass. Anesth Analg 1991;72:428–34.

Benefits from the use of glucose-containing intravenous and priming solutions during coronary artery bypass operation have not been documented, but an increased risk of postoperative neurologic deficit by hyperglycemia has been suggested. To determine benefits, 107 patients undergoing coronary artery bypass operation were managed identically except that one group ($n = 54$) received 5% dextrose in lactated Ringer's solution (D5LR) as the sole intravenous and priming solution during operation and a second group ($n = 53$) received the same solution without glucose (LR). During cardiopulmonary bypass, the D5LR group required significantly less additional crystalloid to maintain safe oxygenator levels and flow (1.8 ± 3.3 vs 15.8 ± 20.9 $mL \cdot kg^{-1} \cdot h^{-1}$) and produced more urine (3.5 ± 3.2 vs 1.2 ± 1.4 $mL \cdot kg^{-1} \cdot h^{-1}$). By 24 h after operation, fluid balance in the LR group was approximately 2 L more positive than in the D5LR group. Five days after operation, the D5LR group weighed less than preoperatively (-0.8 ± 2.6 kg), whereas the LR group gained weight ($+1.0 \pm 2.8$ kg). We conclude that use of glucose-containing solutions during coronary artery bypass operation benefits patients by decreasing perioperative fluid requirements and postoperative fluid retention. Because embolism is the cause of most postoperative neurologic deficits, any increased risk by hyperglycemia is small.

Key Words: ANESTHESIA, CARDIOVASCULAR. SURGERY, CARDIOVASCULAR—cardiopulmonary bypass. FLUID BALANCE, GLUCOSE. METABOLISM, GLUCOSE.

A recent review (1) of the intraoperative use of glucose-containing intravenous solutions recommended that blood glucose be kept under 200 mg/dL in patients undergoing coronary artery bypass operations (CABG) to reduce the magnitude of central nervous system (CNS) deficits that occur postoperatively in a small portion of patients. The recommendation was based on data from nonsurgical patients that suggested CNS deficits after stroke were greater in patients with high blood glucose levels at the time of injury compared with those with lower glucose levels. No data, however, specifically relate this relationship to patients undergoing cardiac operations.

Since the introduction of non-blood priming solutions for extracorporeal circuits 30 yr ago, we have used glucose-containing solutions as the sole priming solution of the cardiopulmonary bypass (CPB) circuit as well as for intravenous solutions during operation. For approximately 20 yr, our standard priming solution has been lactated Ringer's with 5% dextrose. Based on nonsystematic observations, we believed the glucose-containing priming solution benefited the patient by decreasing the volume of additional crystalloid required during perfusion to maintain safe oxygenator volume and adequate flow. To document this observation, we compared in the present study lactated Ringer's solution with 5% dextrose (D5LR) and without 5% dextrose (LR) as the sole priming and intravenous solution for patients undergoing CABG operations to determine if added glucose was advantageous. The postulated but undemonstrated risk of hyperglycemia in these patients could then be evaluated in the light of any demonstrated benefits of added glucose.

Methods

This study was approved by our institutional review board. All patients scheduled for elective primary CABG without additional procedures were eligible for study. Patients with insulin-dependent diabetes mellitus were excluded because their blood glucose

---

Received from the Division of Cardiovascular Anesthesiology, Texas Heart Institute, Houston, Texas. Accepted for publication October 5, 1990.

Address correspondence to Dr. Metz, Cardiovascular Anesthesiology, Texas Heart Institute, P.O. Box 20345, Houston, TX 77225-0345.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

levels would confound data for nondiabetics. Patients over 75 yr old and those with preexisting CNS deficits were also excluded because these characteristics predispose to CNS deficits after CPB (2). One hundred twenty patients were admitted to the study. First scheduled patients of each operative day were alternately assigned to receive either LR or D5LR as intravenous infusion during operation and as priming solution of the extracorporeal circuit. Treatment was assigned alternately by the research assistant responsible for data collection who was unaware of preoperative patient characteristics. Anesthesia was administered by seven different anesthesiologists who, because of patient care considerations, knew the composition of the priming solutions. Patients were otherwise managed by a uniform anesthetic and surgical technique. Bifrontal electroencephalogram, seven-lead electrocardiogram, intraarterial blood pressure, and nasopharyngeal temperature were monitored continuously; arterial blood gas tensions were monitored intermittently. Anesthesia was induced with 0.2 mg/kg diazepam and 0.015 mg/kg fentanyl intravenously. Pancuronium (0.15 mg/kg) was given to facilitate tracheal intubation. Enflurane and 50% nitrous oxide were administered as required to maintain anesthesia and control hypertension.

Cardiopulmonary bypass circuits were primed with 20 mL/kg of assigned crystalloid with 2500 U/L heparin. The same solution without heparin was added as necessary to maintain flow above 40 $mL \cdot kg^{-1} \cdot min^{-1}$ during CPB. According to our perfusion protocol, the minimum safe reservoir volume is 400 mL plus enough volume to flow 15 s at 40 $mL \cdot kg^{-1} \cdot min^{-1}$. When the venous reservoir volume fell below this safe level, the anesthesiologist was notified. Depending on stage of operation, the anesthesiologist elected to add none, 300, or 500 mL of crystalloid to the CPB circuit. Arterial filters were not used. Heparin (300 U/kg) was administered intravenously before aortic cannulation. Anesthesia during CPB was maintained with intermittent doses of thiopental. During CPB, mean arterial pressures less than 40 mm Hg were increased with phenylephrine and pressures greater than 90 mm Hg were decreased with trimethaphan. Patients were cooled to 28°–34°C during CPB. All patients received 500 mL of a D5LR cardioplegic solution. After CPB, anesthesia was maintained with enflurane in oxygen as required. Heparin was reversed with protamine, 1–2 mg per 100 U of heparin. All perfusate remaining in the CPB circuit after decannulation was returned to the patient. No colloid was given intraoperatively.

Glucose, plasma osmolality, and hemoglobin levels were measured 15 min after induction of anesthesia, 5 min after the start of CPB ("early CPB") and at the end of CPB ("late CPB"), and upon arrival in the intensive care unit (ICU). Blood was sampled from the radial artery cannula. Glucose was measured with a Beckman Glucose Analyzer, osmolality with an Advanced Digamatic Osmometer (freezing point depression principle), and hemoglobin with a Coulter Hemoglobinometer. Glucose values above 1000 mg/dL, the maximum value of the analyzer, were considered to be 1000 mg/dL.

Postoperatively, 5% dextrose in 0.25% normal saline was infused in all patients. Operative and 24-h ICU fluid balances were recorded. Fluid balance in the ICU was determined by adding all intravenous fluid and blood products administered in the ICU and subtracting urine output and blood loss through chest tubes. Each patient was weighed preoperatively and on the fifth postoperative day.

Because of the confounding effects of low cardiac output states and transfusion on intraoperative fluid balance, patients given packed red blood cells during operation or requiring an intraaortic balloon pump for weaning were excluded from further study. Thirteen patients, one who required an intraaortic balloon pump and 12 who received blood transfusion (7 in the D5LR group and 5 in the LR group) were excluded.

Data are presented as mean ± SD. Statistical analyses were by paired and unpaired two-tailed *t*-tests as appropriate.

Results

One hundred seven patients, 54 in the D5LR group and 53 in the LR group, completed the study. The groups did not differ in mean age, mean weight, sex distribution, or presence of left ventricular dysfunction assessed by preoperative ejection fraction. Duration of CPB was 55 ± 21 min (range, 17–165 min) for all patients and was not different between groups. As expected, glucose levels were higher in the D5LR group than in the LR group at all periods (Table 1). Glucose levels in both groups increased significantly at the start of CPB, decreased slightly by the end of CPB, and decreased significantly by arrival in the ICU. Changes in plasma osmolality paralleled changes in glucose levels (Table 1, Figure 1). Mean hemoglobin levels of all patients decreased from a postinduction value of 12.5 ± 1.4 g/dL to 7.8 ± 1.1 g/dL during early CPB as a consequence of hemodilution. Hemoglobin then increased to 8.2 ± 1.1 g/dL by the end of CPB and to 10.8 ± 1.4 g/dL upon arrival in the ICU. Differences in hemoglobin between the LR and D5LR groups were not significant at any measurement period.

Table 1. Glucose Level and Osmolality of Patients Undergoing Coronary Artery Bypass Operation and Given Lactated Ringer's Solution With or Without Glucose

	Glucose	No glucose
Number of patients	54	53
Glucose (mg/dL)		
Postinduction	278 ± 91	107 ± 53
Early CPB	836 ± 99	240 ± 57
Late CPB	680 ± 117	217 ± 71
ICU	404 ± 162	187 ± 67
Osmolality (mosm/kg)		
Postinduction	295 ± 6	286 ± 5
Early CPB	313 ± 8	291 ± 6
Late CPB	309 ± 9	288 ± 5
ICU	300 ± 9	285 ± 5

CPB, cardiopulmonary bypass; ICU, intensive care unit.
All values are expressed as mean ± SD.
All values between the two groups are significantly different ($P < 0.001$).

To maintain adequate flows during CPB, patients in the LR group required 1.0 L more additional crystalloid than patients in the D5LR group (Table 2). Despite added crystalloid, urine output of the LR group was only one-third that of the D5LR group. By the end of operation, the LR group had received 1.2 L more crystalloid, excreted 400 mL less urine, and had a 1.5 L more positive water balance than the D5LR group, despite similar blood losses. During the ICU period, volumes of transfused blood, infused crystalloid solutions, and blood loss were comparable in the two groups (Table 3). Although the D5LR group excreted more urine in the ICU, this difference was not significant. By the end of the 24-h ICU period, perioperative fluid balance in the LR group exceeded the D5LR group by 2.0 L ($P < 0.01$). Five days after operation, patients in the LR group weighed almost 2 kg more than their cohorts in the D5LR group ($P < 0.001$) and 1.0 kg more than their preoperative weight.

Twenty-seven patients in the D5LR group and 25 in the LR group required boluses of inotropic drugs for weaning from CPB, and two patients in the LR group required temporary infusions of inotropes to maintain blood pressure during the early postoperative period. Approximately 30% of patients in both groups were treated with single doses of furosemide for transient oliguria during the first 24 h. Differences in duration of tracheal intubation, ICU stay, and hospitalization could not be demonstrated in these small groups. One patient in the LR group suffered a left-sided hemiparesis present on emergence from anesthesia that persisted until discharge 8 wk later. A second patient in the LR group suffered hallucinations on emergence from anesthesia that persisted until the fifth postoperative day. No patient in the D5LR group suffered comparable CNS complications, and there were no hospital deaths in either group.

Discussion

The risk of adding glucose to CPB priming solutions (1,3,4) was inferred from a postulated relationship between hyperglycemia at the time of CNS injury and the severity of the resulting neurologic deficit in diabetic patients suffering ischemic and hemorrhagic strokes. Not only were diabetic patients found to be at greater risk for stroke than nondiabetics, their CNS deficits and mortality subsequent to stroke were greater (3,5–8). In addition, higher blood glucose levels at the time of hospital admission for stroke were associated with higher mortality and more severe deficits (3,9). These clinical observations suggested a relationship between preexisting hyperglycemia and the extent of neurologic damage (3,10). Other observations, however, argue against this relationship. Diabetics may be at greater risk for worse outcome not because of chronic hyperglycemia, but because chronic changes in cerebral autoregulation (11), increased blood viscosity (12), hypercoagulability (13), increased platelet adhesiveness (14), and abnormal endothelial cell function (15) are abnormalities typically associated with diabetics. These disease factors not only predispose to stroke but tend to increase the extent of injury when stroke occurs, independent of blood glucose. No data in any select group of patients suggest that prevention of hyperglycemia before injury or that therapy to lower elevated blood glucose after injury improves outcome (16). In addition, it is not clear whether the hyperglycemia observed at hospital admission was present before injury or was a response to injury. Studies in patients not known to be diabetic who were first seen after head trauma or cardiac arrest demonstrated that higher admission glucose levels predicted greater brain injury (17–20), suggesting that the magnitude of the insult produced a proportional hyperglycemic response rather than the reverse.

Studies in animals clearly demonstrate that hyperglycemia induced by glucose administration before transient global ischemia worsens neurologic outcome and increases the mass of irreversibly damaged brain tissue (21–26). Similarly, animal models of focal cerebral ischemia followed by immediate reperfusion demonstrate greater neuronal damage in the presence of preexisting hyperglycemia (27). When focal injuries are not followed by reperfusion, however, preexisting hyperglycemia either does not affect outcome (28) or improves outcome (29–32). In one study

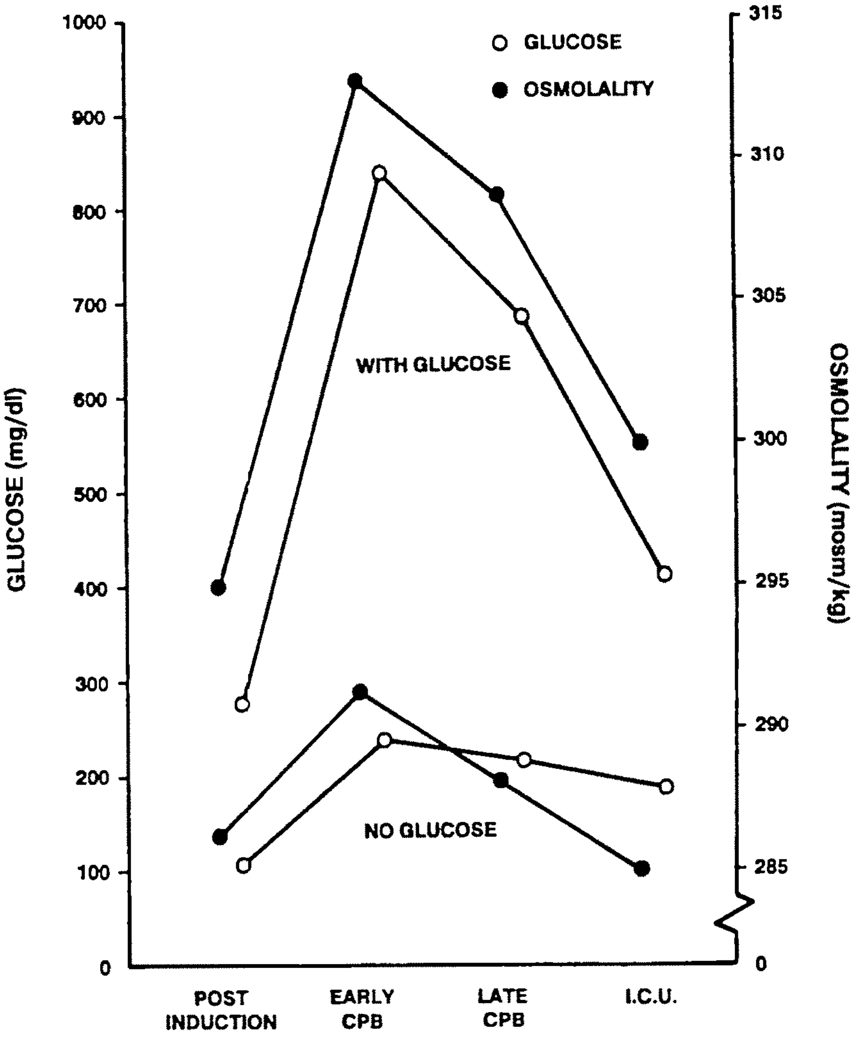


Figure 1. Intraoperative peripheral arterial glucose levels and osmolality during CABG in patients given lactated Ringer's solution with or without glucose as intravenous infusion and oxygenator priming solution. At all sampling periods the mean glucose and osmolality values are significantly different between groups with and without glucose.

of middle cerebral artery occlusion without reperfusion, cats who did not receive exogenous glucose but with high endogenous glucose levels at the time of occlusion had better neurologic outcome than those with lower endogenous glucose levels (32).

Animal data therefore suggest that CNS deficits after global and focal ischemic injuries are greater in the presence of preexisting hyperglycemia only when followed by immediate reperfusion. Focal CNS injuries not followed by immediate reperfusion are either unaffected or improved by preexisting hyperglycemia. Some clinical data also support these observations. Patients suffering from transient global ischemia secondary to cardiac arrest, severe hypotension, or hemorrhage had worse outcomes if their initially observed glucose levels were high (17–20). This relationship, however, did not hold for patients with lacunar infarctions or other focal insults not followed by reperfusion (33,34).

Table 2. Intraoperative Fluid Balance Characteristics of Patients Undergoing Coronary Artery Bypass Operation With Administration of Lactated Ringer's Solution With or Without Glucose

	Glucose	No glucose
Number of patients	54	53
During CPB		
Crystalloid added (mL)	144 ± 270	1147 ± 1149[a]
$(\text{mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1})$	1.8 ± 3.3	15.8 ± 20.9[a]
Urine output (mL)	263 ± 246	94 ± 120[a]
$(\text{mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1})$	3.5 ± 3.2	1.2 ± 1.4[a]
Intraoperative (including CPB)		
Crystalloid (mL)	4253 ± 930	5434 ± 1293[a]
Urine output (mL)	937 ± 481	537 ± 370[a]
Blood loss (mL)	535 ± 197	597 ± 222
Fluid balance (mL)	+2821 ± 805	+4336 ± 1278[a]
(mL/kg)	+34 ± 11	+54 ± 20[a]

CPB, cardiopulmonary bypass.
Values are expressed as mean ± SD.
[a] Significant difference between groups, $P < 0.001$.

Table 3. Postoperative Fluid Balance Characteristics of Patients Undergoing Coronary Artery Bypass Operation With Administration of Lactated Ringer's Solution With or Without Glucose

	Glucose	No glucose
Postoperative		
Crystalloid and colloid (mL)	7581 ± 1689	7596 ± 2487
Blood products (mL)	205 ± 413	340 ± 832
Urine output (mL)	2983 ± 1065	2471 ± 1230
Chest tube loss (mL)	810 ± 552	966 ± 634
Fluid balance (mL)	+4011 ± 1390	+4529 ± 2229
(mL/kg)	+50 ± 19	+56 ± 27
Total (operative and 24 h ICU)		
(mL)	6832 ± 1775	8865 ± 2789[a]
(mL/kg)	84 ± 26	115 ± 38[a]
Weight change day 5 (kg)	−0.8 ± 2.6	+1.0 ± 2.8[b]

ICU, intensive care unit.
Values are expressed as mean ± SD.
[a] Significant difference between groups, $P < 0.01$.
[b] Significant difference between groups, $P < 0.001$.

Based on these observations, patients at risk for global ischemic brain injury followed by reperfusion, such as those undergoing intraoperative elective circulatory arrest, may benefit by prevention of intraoperative hyperglycemia. However, the vast majority of CNS deficits appearing after operations requiring CPB are of embolic origin (2,35,36), producing focal lesions not followed by immediate reperfusion. Under these circumstances, neither animal nor human data support the hypothesis that hyperglycemia from added glucose would worsen neurologic outcome after CPB.

On the other hand, significant benefit accrued to our patients who received glucose-containing solutions in that they required 1 L less added crystalloid to maintain adequate perfusion flow. We speculate that deliberate hyperglycemia produces a parallel increase in osmolality (Figure 1) that reduces translocation of water from intravascular into extracellular spaces during CPB, thus encouraging diuresis during and soon after CPB. This reduction in fluid requirements during CPB by addition of glucose contrasts to the absence of similar reduction in fluid requirements by the addition of 5% albumin (37,38), 20% albumin (39), 25% albumin (40), salt-poor albumin (41), hetastarch (38), or mannitol (42). Neither alterations in colloid oncotic pressure nor addition of mannitol appears to affect fluid requirements during CPB in the manner of glucose.

Glucose-containing priming solutions for CPB are also purported to produce hyperosmolar coma and cause failure to waken after cardiac operations (43,44). Although hyperglycemia is common in hyperosmolar coma, severe dehydration and large increases in serum osmolality are the critical factors in its development (45–47). Arieff and Carroll (46) reported an average osmolality of 384 mosm/kg in 37 patients with hyperosmolar coma, with no value under 350 mosm/kg. Gerich et al. (48) reported an average osmolality of 373 mEq/L in 20 patients with hyperosmolar coma. All patients in both reports required days to weeks of polyuria to produce dehydration severe enough to precipitate coma. More than half of these patients were not diabetic and suffered hyperosmolar coma from hyperalimentation coupled with vigorous diuretic therapy. By contrast, mean osmolality in our patients receiving glucose was 313 mosm/L, similar to that reported by Verska (49) and Milam (50) and their associates in patients receiving glucose during CPB. Although marked hyperglycemia occurs both during CPB and in hyperosmolar coma, dehydration leading to coma is not a consequence of CPB regardless of glucose level.

In this study, we demonstrated a clinically important benefit of glucose-containing priming solutions in patients undergoing CABG operations. This benefit was a significant reduction in perioperative fluid requirements and a reduction in postoperative fluid retention. Because most CNS injuries during operations requiring CPB are embolic in origin producing permanent focal injury, added glucose would not be expected to worsen neurologic outcome in those patients with cerebral embolism. Given these demonstrated benefits to all patients undergoing CPB and an undocumented risk to the rare patient who may suffer global ischemia during CPB, we continue to use glucose-containing solutions in operations requiring CPB. Our data do not apply to the broader question of whether all surgical patients should be normoglycemic in the event of unanticipated circulatory collapse causing transient global ischemia. A proper study to answer this question would require knowledge of a critical glucose level that does not worsen neurologic outcome and an anesthetic technique that reliably prevents the hyperglycemic response to surgical stress.

References

1. Sieber FE, Smith DS, Traystman RJ, Wollman H. Glucose: a reevaluation of its intraoperative use. Anesthesiology 1987;67:72–81.
2. Gardner TJ, Horneffer PJ, Manolio TA, et al. Stroke following coronary artery bypass grafting: a ten-year study. Ann Thorac Surg 1985;40:574–81.
3. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 1983;74:540–4.

4. McKnight CK, Elliott MJ, Pearson DT, Holden MP, Alberti GMM. The effects of four different crystalloid bypass pump-priming fluids upon the metabolic response to cardiac operation. J Thorac Cardiovasc Surg 1985;90:97–111.
5. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA 1979;241:2035–8.
6. Asplund K, Hagg E, Helmers C, Lithner F, Strand T, Wester PO. The natural history of stroke in diabetic patients. Acta Med Scand 1980;207:417–24.
7. Wolf PA, Kannel WB, Verter J. Current status of risk factors for stroke. Neurol Clin 1983;1:330–1.
8. Oppenheimer S, Hoffbrand BI, Oswald GA, Yudkin JS. Diabetes mellitus and early mortality from stroke. Br Med J 1985;291:1014–5.
9. Cox NH, Lorains JW. The prognostic value of blood glucose and glycosylated haemoglobin estimation in patients with stroke. Postgrad Med J 1986;62:7–10.
10. Plum F. What causes infarction in ischemic brain? The Robert Wartenberg Lecture. Neurology 1983;33:222–33.
11. Bentsen N, Larsen B, Lassen N. Chronically impaired autoregulation of cerebral blood flow in long term diabetics. Stroke 1975;6:497–502.
12. Barnes AJ, Dormandy TL, Dormandy JA, Slack J. Is hyperviscosity a treatable component of diabetic microcirculatory disease? Lancet 1977;ii:789–91.
13. Ceriello A. Heparin preserves antithrombin III biological activity from hyperglycemia induced alteration in insulin-dependent diabetes. Haemostasis 1986;16:458–64.
14. Colwell JA, Nair RMG, Halushka PV, Rogers C, Whetsell A, Sagel J. Platelet adhesion and aggregation in diabetes mellitus. Metabolism 1979;28:394–400.
15. Porta M, LaSelva M, Molinatti P, Molinatti GM. Endothelial cell function in diabetic microangiopathy. Diabetologia 1987; 30:601–9.
16. Helgason CM. Blood glucose and stroke. Stroke 1988;19:1049–53.
17. Longstreth WT, Inui TS. High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. Ann Neurol 1984;15:59–63.
18. Longstreth WT, Diehr P, Cobb LA, Hanson RW, Blair APL. Neurologic outcome and blood glucose levels during out-of-hospital cardiopulmonary resuscitation. Neurology 1986;36: 1186–91.
19. Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycemia in acute stroke. Arch Neurol 1985;42:661–3.
20. Young B, Ott L, Dempsey R, Haack D, Tibbs P. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. Ann Surg 1989;210:466–73.
21. Myers RE, Yamaguchi S. Nervous system effects of cardiac arrest in monkeys. Arch Neurol 1977;34:65–74.
22. Siemkowicz E, Hansen A. Clinical restitution following cerebral ischemia in hypo-, normo- and hyperglycemic rats. Acta Neurol Scand 1978;58:1–8.
23. Ginsberg MD, Welsh FA, Budd WW. Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat: I. Local cerebral blood flow and glucose utilization. Stroke 1980;11:347–54.
24. Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in rats. Neurology 1982;32:1239–46.
25. D'Alecy LG, Lundy EF, Barton KJ, Zelenock GB. Dextrose containing intravenous fluid impairs outcome and increases death after eight minutes of cardiac arrest and resuscitation in dogs. Surgery 1986;100:505–11.
26. Lanier WL, Strangland KJ, Scheithauer BW, Milde JH, Michenfelder JD. The effect of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: examination of a model. Anesthesiology 1987;66:39–48.
27. Nedergaard M. Transient focal ischemia in hyperglycemic rats is associated with increased cerebral infarction. Brain Res 1987;408:79–85.
28. Nedergaard M, Diemer NH. Focal ischemia of the rat brain, with special reference to the influence of plasma glucose concentration. Acta Neuropathol 1987;73:131–37.
29. Nedergaard M, Astrup J. Infarct rim: effect of hyperglycemia on direct current potential [^{14}C]2-deoxyglucose phosphorylation. J Cereb Blood Flow Metab 1986;6:607–15.
30. Ginsberg MD, Prado R, Dietrich WD, Busto R, Watson BD. Hyperglycemia reduces the extent of cerebral infarction in rats. Stroke 1987;18:570–4.
31. Kraft SA, Larson CP, Shuer LM, Steinberg GK, Benson GV, Pearl RG. Effect of hyperglycemia on neuronal changes in a rabbit model of focal cerebral ischemia. Stroke 1990;21:447–50.
32. Zasslow MA, Pearl RG, Shuer LM, Steinberg GK, Lieberson RE, Larson CP. Hyperglycemia decreases acute neuronal ischemic changes after middle cerebral artery occlusion in cats. Stroke 1989;20:519–23.
33. Chambers BR, Norris JW, Shurvell BL, Hachinski VC. Prognosis of acute stroke. Neurology 1987;37:221–5.
34. Adams HP, Olinger CP, Marler JR, et al. Comparison of admission serum glucose concentration with neurologic outcome in acute cerebral infarction: a study in patients given naloxone. Stroke 1988;19:455–8.
35. Slogoff S, Girgis KZ, Keats AS. Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass. Anesth Analg 1982;61:903–11.
36. Parker FB, Marvasti MA, Bove EL. Neurologic complications following coronary artery bypass. The role of atherosclerotic emboli. Thorac Cardiovasc Surg 1985;33:207–9.
37. Hallowell P, Bland JHL, Dalton BC, et al. The effect of hemodilution with albumin or Ringer's lactate on water balance and blood use in open-heart surgery. Ann Thorac Surg 1978;25:22–9.
38. Sade RM, Stroud MR, Crawford FA, Kratz JM, Dearing JP, Bartles DM. A prospective randomized study of hydroxyethyl starch, albumin, and lactated Ringer's solution as priming fluid for cardiopulmonary bypass. J Thorac Cardiovasc Surg 1985; 89:713–22.
39. Ohqvist G, Settergren G, Lundberg S. Pulmonary oxygenation, central haemodynamics and glomerular filtration following cardiopulmonary bypass with colloid or non-colloid priming solution. Scand J Thorac Cardiovasc Surg 1981;15:257–62.
40. Marelli D, Paul A, Samson R, Edgell D, Angood P, Chiu RC. Does the addition of albumin to the prime solution in cardiopulmonary bypass affect clinical outcome? J Thorac Cardiovasc Surg 1989;98:751–6.
41. Marty AT, Prather J, Matloff JM, Schauble J. Oncotic effects of dilutional bypass, albumin, and diuretics. Arch Surg 1973;107: 21–5.
42. Utley JR, Stephens DB, Wachtel C, et al. Effect of albumin and mannitol on organ blood flow, oxygen delivery, water content, and renal function during hypothermic hemodilution cardiopulmonary bypass. Ann Thorac Surg 1982;33:250–7.
43. Brenner WI, Lansky Z, Engelman RM, Stahl WM. Hyperosmolar coma in surgical patients: an iatrogenic disease of increasing incidence. Ann Surg 1972;178:651–4.
44. Mills NL, Beaudet RL, Isom OW, Spencer FC. Hyperglycemia during cardiopulmonary bypass. Ann Surg 1973;175:203–5.
45. Greenstein AJ, Dreiling DA. Nonketotic hyperosmolar coma in the postoperative patient. Am J Surg 1971;121:678–701.

46. Arieff AI, Carroll HJ. Nonketotic hyperosmolar coma with hyperglycemia. Medicine 1972;51:73–84.

47. Bivins BA, Hyde GL, Sachatello CR, Griffen WO. Physiopathology and management of hyperosmolar hyperglycemic nonketotic dehydration. Surg Gynecol Obstet 1982;154:534–40.

48. Gerich JE, Martin MM, Recant L. Clinical and metabolic characteristics of hyperosmolar nonketotic coma. Diabetes 1971;20:228–38.

49. Verska JJ, Ludington LG, Brewer LA. A comparative study of cardiopulmonary bypass with non-blood and blood prime. Ann Thorac Surg 1974;18:72–80.

50. Milam JD, Austin SF, Martin RF, Keats AS, Cooley DA. Alteration of coagulation and selected clinical chemistry parameters in patients undergoing open heart surgery without transfusions. Am J Clin Pathol 1981;76:155–62.

ANESTH ANALG 1991;72:435–9

Roles of β_1- and β_2-Adrenoceptors in the Mechanism of Halothane Myocardial Sensitization in Dogs

Yukio Hayashi, MD, Koji Sumikawa, MD, Masakazu Kuro, MD, Kazuo Fukumitsu, MD, Chikara Tashiro, MD, and Ikuto Yoshiya, MD

HAYASHI Y, SUMIKAWA K, KURO M, FUKUMITSU K, TASHIRO C, YOSHIYA I. Roles of β_1- and β_2-adrenoceptors in the mechanism of halothane myocardial sensitization in dogs. Anesth Analg 1991;72:435–9.

The authors investigated the comparative roles of β_1- and β_2-adrenoceptors in myocardial sensitization by halothane in dogs. The arrhythmogenic dose (AD) of isoproterenol was determined in the presence of various doses of phenylephrine during halothane anesthesia in dogs, and the influences of 1-metoprolol (β_1-antagonist) and ICI-118,551 (β_2-antagonist) on the AD were examined. In the presence of 1-metoprolol, the AD of isoproterenol was significantly greater than the control, but in the presence of ICI-118,551, the AD of isoproterenol was lower. Blood pressure during the arrhythmias was higher in the presence of ICI-118,551 than that in controls. In addition, the AD of ritodrine (β_2-agonist) was also determined at various doses of phenylephrine. The interaction between phenylephrine and ritodrine in inducing arrhythmias showed hyperbolic isoboles. However, 1-metoprolol completely inhibited the occurrence of arrhythmias induced by ritodrine and phenylephrine. The results suggest that myocardial β_1-adrenoceptors play an essential role in the genesis of arrhythmias during halothane anesthesia in dogs, whereas β_2-adrenoceptors do not.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART, ARRHYTHMIA. PHARMACOLOGY, PHENYLEPHRINE, ISOPROTERENOL, RITODRINE, METOPROLOL, ICI-118,551. RECEPTORS, β-ADRENERGIC.

The distribution of β-adrenoceptor subtypes has significant clinical relevance to the therapeutic usage of β-blockers (1). β-Receptors in the heart were originally considered to be β_1-receptors (2). In fact, metoprolol, a selective β_1-blocker (3), has been shown to be effective in preventing epinephrine-induced arrhythmias during halothane anesthesia (4). However, β_2-adrenoceptors also are present in the heart of vertebrates (5–7). Moreover, it has been considered that β_2-receptors mediate positive chronotropic action, and they are classified as relatively epinephrine-selective as compared with norepinephrine (8). Therefore, cardiac β_2-receptors might play a role in the genesis of ventricular arrhythmias induced by epinephrine and halothane. This study was carried out to clarify the relative contributions of the β_1- and β_2-adrenoceptors in epinephrine-induced arrhythmias during halothane anesthesia.

Materials and Methods

Seventy mongrel dogs of either sex, weighing between 8 and 12 kg, were used in 225 experiments. Whenever different experiments were performed with the same dog, more than 7 days was allowed to elapse between one experiment and the next. Anesthesia was induced with halothane alone and maintained at an end-tidal concentration of 1.3 MAC (1.1%), which was continuously measured by an anesthetic gas analyzer (Datex AA 102-30-00, Helsinki, Finland). The trachea of each dog was intubated with a cuffed endotracheal tube, and the lungs were mechanically ventilated with air (Aika R60, Tokyo, Japan). The end-tidal carbon dioxide concentration was continuously monitored with an expired gas monitor (Minato 1H 21A, Osaka, Japan) and maintained at a level of 35–40 mm Hg. A heating

---

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from the Department of Anesthesiology, National Cardiovascular Center, Osaka, Japan; the Department of Anesthesiology, Osaka University Medical School, Osaka, Japan; and the Department of Anesthesiology, Osaka Medical Center and Institute for Maternal and Child Health, Osaka, Japan. Accepted for publication November 15, 1990.

Address correspondence to Dr. Hayashi, Department of Anesthesiology, National Cardiovascular Center, 5-7-1 Fujishiro-dai Suita, Osaka 565, Japan.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

lamp and a circulating water blanket were used to maintain esophageal temperature between 37.0 and 38.5°C. Lead II of the electrocardiogram was monitored continuously. A femoral artery catheter was inserted for monitoring blood pressure and for obtaining blood samples. A femoral vein was cannulated for the administration both of drugs and of a solution of 3% dextrose in 0.5% NaCl. The latter was infused at a rate of about 10 $mL \cdot kg^{-1} \cdot h^{-1}$. Serum levels of K^+ were maintained between 3.5 and 4.5 mEq/mL by infusing K^+ at a rate of 1–10 mEq/h. Arterial pH, Po_2, and serum Na^+ were maintained within the range of 7.35–7.45, 85–100 mm Hg, and 135–150 mEq/L, respectively.

The drugs used in this experiment were phenylephrine as an α_1-agonist, isoproterenol as a β-agonist, ritodrine as a selective β_2-agonist (1), 1-metoprolol as a selective β_1-antagonist, and ICI 118,551 as a selective β_2-antagonist (9).

The arrhythmogenic dose (AD) of each adrenoceptor agonist was determined as follows. The AD was defined as the dose that produced four or more premature ventricular concentrations within 15 s (10). The AD was determined in each dog, and the mean AD value was calculated. The AD of isoproterenol combined with phenylephrine was determined as described previously (11). Isoproterenol was injected at logarithmically spaced increasing doses in the presence of different doses of phenylephrine until the AD was reached. In this experiment, isoproterenol was injected 10 s after the administration of phenylephrine. The AD of isoproterenol combined with phenylephrine was determined under three different conditions: in the presence of 1-metoprolol (0.4 mg/kg); in that of ICI-118,551 (0.2 mg/kg); or with no antagonist (control). These antagonists were administered before phenylephrine and isoproterenol injections, and no additional dose was administered.

The AD of ritodrine combined with phenylephrine was also determined to evaluate the role of β_2-adrenoceptors directly. This experiment was performed in both the absence and presence of 1-metoprolol (0.4 mg/kg) to exclude the possibility of β_1-adrenergic action.

The data were expressed as mean ± SEM. The results of multiple groups were analyzed by one-way analysis of variance, and comparisons between groups were assessed by Student's *t*-test with Bonferroni correction. Student's *t*-test for unpaired data was used for comparisons between two groups. P values <0.05 were considered to be statistically significant.

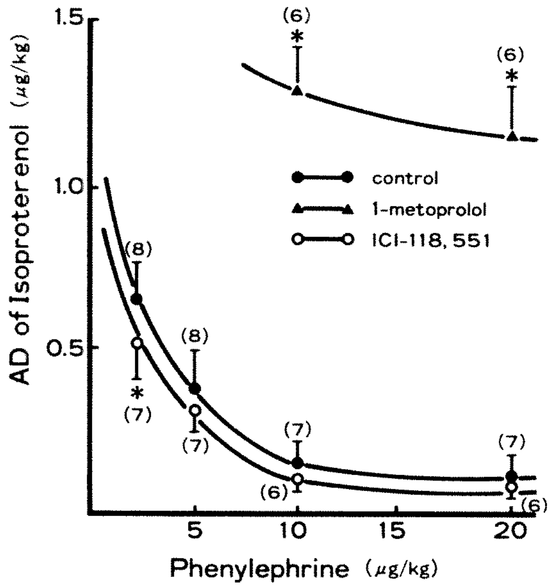


Figure 1. The isoboles plotting arrhythmogenic doses of isoproterenol against various doses of phenylephrine to induce arrhythmias during halothane anesthesia in the presence of 1-metoprolol (β_1-antagonist), ICI-118,551 (β_2-antagonist), or in the absence of a β-antagonist (control) (mean ± SEM; number is shown in parentheses). $*P < 0.05$ compared with control value.

Results

Figure 1 shows the isoboles plotting the AD of isoproterenol against the varying doses of concomitantly administered phenylephrine in the presence of 1-metoprolol and ICI-118,551 and in the absence of any antagonist (control). ICI-118,551 significantly decreased the AD of isoproterenol at a phenylephrine dose of 2.5 μg/kg; at the other phenylephrine doses it tended to decrease the AD of isoproterenol, although there was no significant difference from control value. On the contrary, 1-metoprolol markedly increased the AD of isoproterenol at phenylephrine doses of 2.5, 5.0, 10, and 20 μg/kg. At phenylephrine doses of 2.5 and 5.0 μg/kg, the AD of isoproterenol was not reached even at the highest dose of 1.6 μg/kg isoproterenol. Thus the AD of isoproterenol at these phenylephrine doses was not shown in Figure 1.

Blood pressure and heart rate at the time of the arrhythmias induced by the concomitant administration of phenylephrine and isoproterenol are shown in Table 1. Both systolic and diastolic arterial pressures at each phenylephrine dose in the presence of ICI-118,551 were significantly higher than those in controls; the heart rate was lower but not significantly so. In the presence of 1-metoprolol, blood pressure and heart rate were not significantly different from control levels.

The AD of ritodrine combined with phenylephrine

Table 1. Effect of 1-Metoprolol and ICI-118,551 on Systolic and Diastolic Arterial Pressures and Heart Rate at the Time of the Arrhythmias Induced With Isoproterenol in Combination With Phenylephrine During Halothane Anesthesia

Phenylephrine (μg/kg)	Control	1-Metoprolol	ICI-118,551
Systolic arterial pressure (mm Hg)			
2.5	132 ± 9.9 (8)	—	172 ± 8.5[a] (7)
5.0	149 ± 11.2 (8)	—	186 ± 8.6[a] (7)
10	163 ± 10.9 (7)	186 ± 4.2 (6)	200 ± 6.2[a] (6)
20	170 ± 4.8 (7)	193 ± 9.6 (6)	223 ± 4.8[b] (6)
Diastolic arterial pressure (mm Hg)			
2.5	59 ± 7.9	—	86 ± 4.2[a]
5.0	67 ± 8.9	—	95 ± 3.9[a]
10	78 ± 5.0	94 ± 7.1	107 ± 5.0[b]
20	81 ± 6.0	91 ± 4.2	121 ± 6.4[b]
Heart rate (beats/min)			
2.5	209 ± 20.2	—	173 ± 11.2
5.0	189 ± 12.0	—	152 ± 11.1
10	166 ± 14.7	151 ± 3.0	151 ± 7.8
20	158 ± 14.3	141 ± 16.4	137 ± 12.4

Values are expressed as mean ± SEM.
[a] $P < 0.05$ compared with control value.
[b] $P < 0.01$ compared with control value.

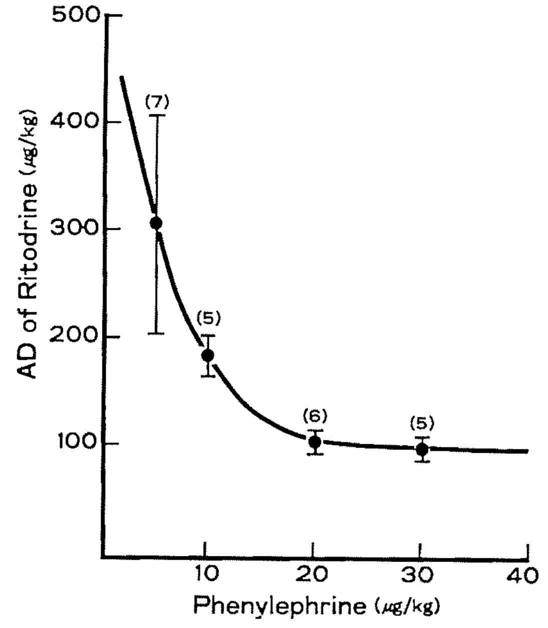


Figure 2. The isoboles plotting arrhythmogenic doses of ritodrine against various doses of phenylephrine required to induce arrhythmias during halothane anesthesia (mean ± SEM; number is shown in parentheses).

is shown in Figure 2. The interaction of phenylephrine and ritodrine in inducing arrhythmias is typically synergistic (12). However, as shown in Table 2, this interaction was not observed in the presence of 1-metoprolol: that is, the AD of ritodrine at phenylephrine doses of 20 and 30 μg/kg was not reached in the presence of 1-metoprolol.

Table 2. The Effect of 1-Metoprolol on the Arrhythmogenic Dose of Ritodrine in Combination With Phenylephrine During Halothane Anesthesia

	AD of ritodrine (μg/kg)	
Phenylephrine (μg/kg)	1-Metoprolol (−)	1-Metoprolol (+)
20	113 ± 19 (6)	1280 < (5)[a]
30	103 ± 20 (5)	1280 < (5)[a]

Values are expressed as mean ± SEM. Number is shown in parentheses.
[a] The arrhythmogenic dose was not reached at doses up to 1280 μg/kg.

Discussion

The mechanism of myocardial sensitization by halothane has been investigated in several ways (4,11,13–17). Adrenoceptor contribution to this phenomenon has been one of the interesting questions to be elucidated. In 1983, contrary to a previous statement that myocardial β-receptors are responsible for myocardial sensitization by halothane (14), Maze and Smith (4) reported that myocardial α_1-receptors play a more important role in halothane-epinephrine arrhythmias. On the other hand, Hayashi et al. (11) found that both α_1- and β-receptor agonists are necessary to induce arrhythmias during halothane anesthesia. Myocardial β-receptors were earlier considered to be of the β_1-type (2). However, it is now recognized not only that β_2-receptors also exist in the heart of vertebrates (5–7) but that they are relatively selective to epinephrine compared with norepinephrine (8). In this study, we examined whether β_2-receptors are involved in the myocardial sensitization by halothane.

As shown in Figure 1, the AD of isoproterenol at a phenylephrine dose of 2.5 μg/kg in the presence of ICI-118,551 was significantly lower than that of the control, and the ADs of isoproterenol at the other phenylephrine doses in the presence of ICI-118,551 tended to be lower than those of the control. On the other hand, the ADs of isoproterenol in the presence of 1-metoprolol were much higher than those of the control at 10 and 20 μg/kg of phenylephrine. These results indicate that β_1-blockade prevents the genesis of the arrhythmias, whereas β_2-blockade might tend to potentiate the arrhythmogenicity rather than attenuate it.

β_2-Receptors are recognized to be present on vascular smooth muscle (2). It is likely that ICI-118,551 prevents the vasodilating effect of β_2-receptors on the vascular smooth muscle resulting in the elevation of blood pressure. In fact, as shown in Table 1, both systolic and diastolic arterial pressures during the arrhythmias in the presence of ICI-118,551 were significantly higher than those of the control. Blood pressure elevation has been regarded as an important factor in the induction of arrhythmias during halothane anesthesia (11,13). Therefore, one possible mechanism by which β_2-blockade tended to potentiate the arrhythmogenicity might be attributable to this blood pressure elevation.

Ritodrine, which is considered to be a relatively selective β_2-adrenoceptor agonist and is frequently used to prevent premature labor (1), synergistically interacts with phenylephrine to induce arrhythmias during halothane anesthesia (Figure 2). However, 1-metoprolol, a β_1-antagonist, completely inhibited the arrhythmogenic action of ritodrine (Table 2). This may be explained on the basis that the ritodrine dosage in this experiment was so great that ritodrine bound not only to β_2- but also to β_1-adrenoceptors, resulting in the induction of arrhythmias.

Sharma (17) reported that propranolol, a nonselective β-antagonist, was effective in preventing epinephrine-induced arrhythmias during halothane anesthesia. On the other hand, Maze and Smith (4) have shown that 1-metoprolol, a selective β_1-antagonist, is also useful in this respect. However, no studies have yet demonstrated which antagonist is more effective for the treatment of halothane-epinephrine arrhythmias. Vincent et al. (18) reported that β_2-antagonists may be useful for cardioprotection because β_2-blockade attenuates the norepinephrine release stimulated by circulating epinephrine via presynaptic β_2-receptors. Propranolol might be superior to 1-metoprolol in this regard. However, the present results show that β_2-blockade is not effective in preventing arrhythmias but rather potentiates the arrhythmias resulting from enhanced blood pressure elevation. Thus, β_1-antagonists appear to be preferable to β_2- or nonselective β-antagonists for the treatment of halothane-epinephrine arrhythmias.

Finally, the applicability of the present results to the clinical situation may be limited owing to the animal model used here. Actually, the vulnerability to myocardial sensitization by halothane differs between dogs and humans because of a species difference (19).

In conclusion, myocardial β_2-adrenoceptors play no role in inducing arrhythmias during halothane anesthesia as compared with the significant role of β_1-adrenoceptors. Indeed, β_2-adrenoceptor antagonists might potentiate the arrhythmias resulting from elevated blood pressure with which they are associated.

The authors acknowledge Ciba-Geigy Ltd. (Tokyo, Japan) for supplying 1-metoprolol and Imperial Chemical Industries (England) for supplying ICI-118,551. They also thank T. Nishimura, T. Konishi, Y. Furukawa, K. Ishida, and K. Yamaoka for their assistance throughout this study.

References

1. Weiner N. Norepinephrine, epinephrine, and the sympathomimetic amines. In: Gilman AG, Goodmann LS, Rall TW, Murad F, eds. The pharmacological basis of therapeutics, 7th ed. New York: Macmillan, 1985:145–80.
2. Land AM, Arnold A, McAuliff JP, Lunduana FP, Brown RC. Differentiation of receptor systems activated by sympathomimetic amines. Nature 1967;214:597–8.
3. Koch-Weser J. Drug therapy: metoprolol. N Engl J Med 1979; 301:698–703.
4. Maze M, Smith SM. Identification of receptor mechanism mediating epinephrine-induced arrhythmias during halothane anesthesia in the dog. Anesthesiology 1983;59:322–6.
5. Brown J, McLeod A, Shand D. Evidence for cardiac β_2-adrenoceptors in man. Clin Pharmacol Ther 1983;33:424–8.
6. Robberecht P, Delhaye M, Taton G, et al. The human heart beta-adrenergic receptors. I. Heterogeneity of the binding sites: presence of 50% beta$_1$- and 50% beta$_2$-adrenergic receptors. Mol Pharmacol 1983;24:169–73.
7. Stile GL, Caron MG, Lefkowitz RJ. β-Adrenergic receptors: biochemical mechanisms of physiological regulation. Physiol Rev 1984;64:661–743.
8. Stene-Larsen G, Ask JA, Helle KB, Fin R. Activation of cardiac beta$_2$ adrenoceptors in the human heart. Am J Cardiol 1986; 57:7F–10F.
9. Donnell SR, Wanstall JC. Evidence that ICI 118,551 is a potent, highly beta$_2$-selective adrenoceptor antagonist and can be used to characterize beta-adrenoceptor populations in tissues. Life Sci 1980;27:671–7.
10. Pace NL, Ohmura A, Wong KC. Epinephrine-induced arrhythmias: effect of exogenous prostaglandins and prostaglandin synthesis inhibition during halothane-O$_2$ anesthesia in the dog. Anesth Analg 1979;58:401–4.

11. Hayashi Y, Sumikawa K, Tashiro C, Yoshiya I. Synergistic interaction of α_1- and β-adrenoceptor agonists on induction arrhythmias during halothane anesthesia in dogs. Anesthesiology 1988;68:902–7.
12. Gero A. Intimate study of drug action. III. Mechanism of molecular drug action. In: Dipalma JR, ed. Drill's pharmacology in medicine. 4th ed. New York: McGraw-Hill, 1971:67–98.
13. Raynold AK. On the mechanism of myocardial sensitization to catecholamines by hydrocarbon anesthesics. Can J Physiol Pharmacol 1984;62:183–98.
14. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. Anesthesiology 1968;29:763–84.
15. Atlee JL, Alexander SC. Halothane effects of conductivity of the AV node and His Purkinje system in the dog. Anesth Analg 1977;56:378–86.
16. Miletich DJ, Khan A, Albrecht RF, Jozefiak A. Use of heart cell cultures as a tool for the evaluation of halothane arrhythmia. Toxicol Appl Pharmacol 1983;70:181–7.
17. Sharma PL. Effect of propranolol on catecholamine-induced arrhythmias during nitrous oxide-halothane anaesthesia in the dog. Br J Anaesth 1966;38:871–7.
18. Vincent HH, Man in't Veld AJ, Boomsma F, Derkx FHM, Wenting GJ, Schalekamp MADH. Cardioprotection by blockade of beta$_2$-adrenoceptors. Eur Heart J 1983;4:109–15.
19. Sumikawa K, Ishizaka N, Suzuki M. Arrhythmogenic plasma levels of epinephrine during halothane, enflurane, and pentobarbital anesthesia in the dog. Anesthesiology 1983;58:322–5.

1991;72:440–8

Effects of Halothane on Hypoxic Pulmonary Vasoconstriction in Canine Atelectasis

David H. Johnson, MD, Tom S. Hurst, BVSc, MVSc, and I. Mayers, MD

JOHNSON DH, HURST TS, MAYERS I. Effects of halothane on hypoxic pulmonary vasoconstriction in canine atelectasis. Anesth Analg 1991;72:440–8.

We studied the interactions of atelectasis and halothane on hypoxic pulmonary vasoconstriction using an isolated canine lobe. We divided pulmonary vascular resistance into arterial, venous, and middle segmental resistances by a vascular occlusion technique. We found that middle segmental resistance significantly increased ($P < 0.05$) from 0.016 ± 0.007 cm $H_2O \cdot mL^{-1} \cdot min^{-1}$ during normoxic ventilation to 0.06 ± 0.007 cm $H_2O \cdot mL^{-1} \cdot min^{-1}$ during hypoxic ventilation. We then produced sublobar atelectasis by introducing 4.5-mm steel ball bearings into the lobar bronchus, which resulted in a significant increase ($P < 0.05$) of middle segmental resistance to 0.046 ± 0.014 cm $H_2O \cdot mL^{-1} \cdot min^{-1}$ during normoxic ventilation and a further significant increase ($P < 0.05$) to 0.084 ± 0.02 cm $H_2O \cdot mL^{-1} \cdot min^{-1}$ during hypoxic ventilation. Ventilation with 2.0% halothane but not 0.5% halothane prevented the increases in middle segmental resistance observed with either atelectasis or hypoxic ventilation. Values of arterial and venous segmental resistances were not similarly affected. We conclude that sublobar atelectasis increases pulmonary vascular resistance by stimulating hypoxic pulmonary vasoconstriction. Both halothane and hypoxia primarily act upon the middle vascular segment, but their effects are in opposite directions and, in the former instance, are concentration-dependent.

Key Words: ANESTHESIA, VOLATILE—halothane. LUNG, BLOOD FLOW—hypoxic pulmonary vasoconstriction.

Anesthesia results in decreased pulmonary compliance, which promotes small airway closure and atelectatic lung areas with decreased ventilation (1). Analysis of ventilation/perfusion (V/Q) ratios in anesthetized patients has shown that increased alveolar-arterial oxygen gradients are due to increased perfusion of low ventilation areas (2–5). Increased maldistribution of perfusion and ventilation also occur in the setting of patchy atelectasis. Although postoperative pulmonary atelectasis is a frequent complication of thoracic or upper abdominal surgery, arterial blood oxygenation is often minimally decreased (6). The homeostatic mechanism preserving arterial oxygenation may be a function of active vasoconstriction of pulmonary vessels with resultant diversion of blood flow away from atelectatic alveoli. By diverting perfusion away from areas of low ventilation or away from areas of intrapulmonary shunt, hypoxic pulmonary vasoconstriction could maintain V/Q ratios near normal and prevent significant decreases in arterial oxygenation. In a canine model of atelectasis, hypoxic pulmonary vasoconstriction rather than mechanical obstruction of the vasculature is probably the predominant mechanism diverting blood flow away from the atelectatic lung (7–9). Because the regional diversion of blood away from low ventilation units is dependent primarily on active vasoconstriction, administration of agents that prevent vasoconstriction should worsen V/Q matching. Halothane may impair the regional control of pulmonary blood flow (10–14), and, therefore, in the setting of atelectasis the administration of halothane might worsen arterial oxygenation.

It is possible to partition pulmonary vascular resistance into arterial, venous, and middle segment resistances by sequentially occluding the artery and vein of an isolated lobe (15). We have previously characterized the effects of halothane in an isolated lung lobe preparation during normoxic and hypoxic ventilation using this technique of vascular occlu-

---

Supported by Saskatchewan Health Research Board and by the ICI Pharmaceuticals Canadian Research Award in Anaesthesia.

Received from the Departments of Anaesthesia and Medicine, University of Saskatchewan and Royal University Hospital, Saskatoon, Saskatchewan, Canada. Accepted for publication November 21, 1990.

Address correspondence to Dr. Johnson, Department of Anaesthesia, Box 95, Royal University Hospital, Saskatoon, Saskatchewan, Canada S7N 0X0.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

sions (14). We found that both halothane and hypoxia act at the level of the middle vascular segment; hypoxia increases middle segment resistance and halothane decreases middle segment resistance. In this current study we extended our previous investigations and have evaluated the changes in pulmonary vascular resistance induced by halothane in a model of sublobar atelectasis (16). Because the efficacy of hypoxic pulmonary vasoconstriction in diverting pulmonary blood flow away from hypoxic regions increases with decreasing size of the hypoxic region, blood flow diversion is maximal with very small hypoxic segments and is nonexistent when the entire lung is made hypoxic (17,18). We would therefore expect that hypoxic pulmonary vasoconstriction could be a potent force to optimize V/Q matching in the presence of patchy atelectasis. In this study we evaluated the role of hypoxic pulmonary vasoconstriction in the presence of sublobar atelectasis and examined the interactions of halothane with hypoxic pulmonary vasoconstriction. These interactions were studied using low (0.5%) and high (2.0%) concentrations of halothane to determine if there was a concentration-dependent effect of halothane on pulmonary vascular resistance.

Methods

Animal Preparation

These studies were carried out with the approval of the University Animal Care Committee. The surgical preparation of the isolated lobe has been described in detail elsewhere (14). In brief, six mongrel dogs (weight, 20–30 kg) were anesthetized (25 mg/kg thiopental), intubated, and ventilated (Harvard ventilator) with room air at a tidal volume of 20 mL/kg. Catheters were inserted into the abdominal aorta via the femoral artery for subsequent removal of blood and into the femoral vein for drug administration. The left upper lobe was surgically removed to facilitate exposure of the left lower lobe. The left lower lobe artery and vein were dissected and cannulated. A No. 6 cuffed tracheal tube was inserted into the lobar bronchus through a bronchotomy. After the cannulae were inserted and the lobe isolated, the animals were killed by injection of 10 mL supersaturated KCl solution. The cannulated lobe was left in situ within the thoracic cavity and was connected to an extracorporeal circuit. The lobe was perfused with 400 mL phlebotomized autologous blood diluted to 500 mL with heparin (1000 U) and normal saline. Pulmonary venous blood passively drained into a venous reservoir and was pumped by a roller pump through a heat exchanger, filter, and bubble deoxygenator (95% N_2, 5% CO_2) and was then returned to the arterial reservoir. The lobar bronchus was ventilated independently of the remainder of the lung by a second Harvard ventilator (V_T = 150–200 mL). Lobar arterial pressure (Pa) and venous pressure (Pv) were adjusted by varying the heights of the respective reservoirs. Lobar arterial and venous pressures were measured at pressure ports near the arterial and venous cannulae, respectively. Airway pressure was measured with an air-phase transducer connected by low-compliance tubing to a port near the endobronchial tube. Before commencing the experimental protocol, at least 30 min was allowed for the preparation to stabilize as assessed by a constant flow ($\dot{Q}_L$) over a 5-min period. Heparin (1000 U) and 50% dextrose (1 mL) were added to the circuit every 30 min.

Calculations

Using methodology similar to that described by Hakim et al. (15), total pulmonary vascular resistance (R_{tot}) was divided into arterial segment resistance (Ra), middle segment resistance (Rm), and venous segment resistance (Rv). We calculated the distribution of resistances using the pressure changes after a venous or arterial occlusion (14). After an arterial occlusion an initial rapid decrease in pressure (ΔPa) followed by a slow decrease in pressure was recorded at the arterial pressure port. Similarly, after venous occlusion we recorded a rapid increase in venous pressure (ΔPv) followed by a slow increase in pressure. Total pulmonary vascular resistance was calculated as $(Pa - Pv)/\dot{Q}_L$. Arterial and venous segment resistances were calculated as $\Delta Pa/\dot{Q}_L$ and $\Delta Pv/\dot{Q}_L$, respectively. Middle segment resistance was calculated as $R_{tot} - (Ra + Rv)$.

Venous admixture (Q_{VA}/Q_T) through the lobe was calculated from the following equation: $Q_{VA}/Q_T = (Cc'o_2 - Cpao_2)/(Cc'o_2 - Cpvo_2)$, where Cxo_2 refers to the content of oxygen in blood and c′ is the end capillary blood, pv is the pulmonary venous blood, and pa is the pulmonary arterial blood. Oxygen contents were calculated from derived oxygen saturations (19) and hemoglobin concentrations. Alveolar Po_2 was calculated using the alveolar gas equation; pulmonary arterial and venous values of Po_2 (Pao_2 and Pvo_2, respectively) were directly measured. Hemoglobin, in turn, was estimated as one-third of the measured hematocrit.

Experimental Protocol

After the stabilization period, baseline flow was set by adjusting Pa to near 20 cm H_2O and Pv to 5 cm H_2O. This ensured zone 3 conditions for flow during the remainder of the experiment. The lobes received five paired periods of ventilation. The lobes were initially ventilated with a control gas mixture (35% O_2, 7% CO_2, 58% N_2) followed by ventilation with a hypoxic gas mixture (3% O_2, 7% CO_2, 90% N_2). After these baseline ventilatory periods with control and hypoxic gas mixtures (period C and period H, respectively), the lobe was denitrogenated by ventilation with 100% O_2 for 10 min. We then produced sublobar atelectasis by introducing steel ball bearings (4.5 mm diameter) into the left lobar bronchus. The ball bearings (range, 20–30) were given in numbers adequate to decrease lobar Pv_{O_2} by 20 mm Hg. After the introduction of the steel ball bearings, tidal volume was reduced to maintain peak inspiratory pressure similar to that measured during period C. After production of atelectasis, the lobes were again ventilated with paired periods of control gas (period CA_1) and hypoxic gas (period HA_1). The lobes were then ventilated with the control gas mixture to which halothane in a concentration of 0.5% (period $CA_{H0.5}$) or 2.0% (period $CA_{H2.0}$) was added. Each control gas ventilation period (periods $CA_{H0.5}$ and $CA_{H2.0}$) was followed by a matched period with the hypoxic gas mixture to which the appropriate concentration of halothane was added (period $HA_{H0.5}$ and period $HA_{H2.0}$, respectively). The order of administration of halothane concentrations (0.5% or 2.0%) was randomized. We used an Ohio halothane vaporizer at a flow of 3 L/min to generate the two concentrations of halothane. After these periods, the lobes received a final paired period of ventilation with the control gas mixture (period CA_2) followed by the hypoxic gas mixture (period HA_2) without any added halothane.

Venous and arterial occlusions were performed in triplicate at the end of each ventilatory period. The occlusions were produced after stopping the ventilator at the end expiration. Immediately preceding the occlusion, blood was withdrawn from the arterial and venous cannulae for blood gas and hematocrit determination. Blood samples were analyzed for Po_2, Pco_2, and pH at 37°C (Corning 162-2) using appropriately calibrated electrodes and were then corrected for blood reservoir temperature (19,20) after calculating hemoglobin saturation from a standard nomogram (19). Inspired gas samples were also withdrawn before occlusions and were analyzed for N_2, O_2, CO_2, and halothane concentrations using a SARA mass spectrometer.

Statistics

Values of blood gas tensions, inspired gas concentrations, and hemodynamic functions were compared between ventilatory periods using a one-way analysis of variance. Where the F statistic showed a significant difference, paired *t*-tests were used to determine which groups were different. Sidak's multiplicative inequality was used to correct for the number of comparisons made between groups (21). Interactions between resistance and venous admixture were evaluated using a linear regression analysis. A P value < 0.05 was considered to show a statistically significant difference. Values are shown as mean ± standard deviations.

Results

By analysis of variance there were no differences between ventilatory periods in temperature, hematocrit, lobar venous and arterial Pco_2, lobar venous and arterial pH, and inspired CO_2 concentrations (see Table 1). Values of F_{IO_2} were similar in all control ventilatory periods and were also similar in all hypoxic ventilatory periods. Because we used a lower F_{IO_2} during the hypoxic periods, the measured values of F_{IO_2} were markedly lower during the hypoxic periods compared with the control periods. Inspired halothane concentrations (FɪHal) were similar in the paired control and hypoxic periods. During periods $CA_{H0.5}$ and $HA_{H0.5}$, the mean values of FiHal were 0.48% ± 0.13% and 0.51% ± 0.10%, respectively. During periods $CA_{H2.0}$ and $HA_{H2.0}$, the mean values of FɪHal were 2.28% ± 0.33% and 2.24% ± 0.32%, respectively. During all other ventilatory periods we did not add halothane to the inspired gases and there was no measurable amount of halothane present.

Table 2 indicates selected blood gas tensions and hemodynamic values. Values of lobar Pa_{O_2} were similar in all 10 ventilatory periods ($P > 0.05$). Values of lobar Pv_{O_2} were similar during the five hypoxic ventilatory periods and were significantly below values during matched control ventilatory periods. Values of Pv_{O_2} were significantly higher during period C (before atelectasis was induced) compared with all other control gas ventilation periods. Because of the small differences in Po_2 between arterial and venous blood during hypoxic periods, Q_{VA}/Q_T was calculated only for control ventilation periods. Values of Q_{VA}/Q_T increased from 9.5% ± 6.0% during period C to 21.8% ± 12.6% during period CA_1 ($P < 0.05$). The addition of halothane (periods $CA_{H0.5}$ and $CA_{H2.0}$) did not result in significant changes in the absolute values of Q_{VA}/Q_T ($P > 0.05$). Venous admixture

Table 1. Controlled Variables for the Ten Ventilatory Periods

	Temp (°C)	Hct (%)	$P\text{vco}_2$ (mm Hg)	$P\text{aco}_2$ (mm Hg)	pvH	paH	$F\text{ico}_2$ (%)	$F\text{io}_2$ (%)	FɪHal (%)
Period C	37 ± 0.5	27 ± 1	45 ± 5	41 ± 5	7.23 ± 0.05	7.28 ± 0.05	6 ± 0.5	31 ± 2	0
Period H	37 ± 0.5	27 ± 1	42 ± 3	40 ± 3	7.29 ± 0.04	7.31 ± 0.04	6 ± 0.5	3.5 ± 1	0
Period CA_1	37 ± 0.5	27 ± 1	44 ± 4	40 ± 1	7.24 ± 0.04	7.30 ± 0.02	6 ± 1	31 ± 1	0
Period HA_1	37 ± 0.5	26 ± 2	41 ± 4	41 ± 2	7.28 ± 0.03	7.29 ± 0.04	6 ± 1	3.5 ± 1	0
Period $CA_{H0.5}$	37 ± 0.5	27 ± 2	43 ± 5	41 ± 2	7.23 ± 0.04	7.28 ± 0.03	6 ± 1	30 ± 2	0.48 ± 0.13
Period $HA_{H0.5}$	37 ± 0.5	27 ± 2	42 ± 2	40 ± 2	7.28 ± 0.03	7.30 ± 0.05	5 ± 1	3.5 ± 1	0.51 ± 0.1
Period $CA_{H2.0}$	37 ± 0.5	26 ± 2	45 ± 6	41 ± 3	7.23 ± 0.03	7.29 ± 0.03	6 ± 1	30 ± 2	2.28 ± 0.33
Period $HA_{H2.0}$	37 ± 0.5	26 ± 2	41 ± 3	40 ± 3	7.27 ± 0.03	7.28 ± 0.04	6 ± 1	3.5 ± 1	2.24 ± 0.32
Period CA_2	37 ± 0.5	26 ± 2	44 ± 5	40 ± 3	7.22 ± 0.02	7.28 ± 0.03	6 ± 1	31 ± 2	0
Period HA_2	37 ± 0.5	26 ± 2	41 ± 2	40 ± 2	7.27 ± 0.04	7.27 ± 0.04	6 ± 1	3.5 ± 1	0

Temp, temperature; Hct, hematocrit; $P\text{vco}_2$, pulmonary venous blood carbon dioxide partial pressure; $P\text{aco}_2$, pulmonary arterial blood carbon dioxide partial pressure; pvH, pulmonary venous pH; paH, pulmonary arterial pH; $F\text{ico}_2$, fraction inspired carbon dioxide; $F\text{io}_2$, fraction inspired oxygen; FɪHal, fraction inspired halothane.

By analysis of variance controlled variables were similar except for $F\text{io}_2$ and FɪHal, which varied by experimental period.

Table 2. Selected Hemodynamic and Blood Gas Tensions for the Ten Ventilatory Periods

	$P\text{ao}_2$ (mm Hg)	$P\text{vo}_2$ (mm Hg)	$\dot{Q}_L$ (mL/min)	Pa (cm H_2O)	Pv (cm H_2O)	Q_{VA}/Q_T (%)
Period C	37 ± 10	115 ± 20	190 ± 17	20.6 ± 0.5	5.0 ± 0.9	9.5 ± 6.0
Period H	29 ± 11	28 ± 6^a	127 ± 22^a	21.2 ± 1.0	4.5 ± 1.1	—
Period CA_1	30 ± 11	77 ± 23^b	136 ± 24^b	21.0 ± 1.3	4.3 ± 1.0	21.8 ± 12.6^b
Period HA_1	22 ± 7	27 ± 7^a	93 ± 10^{a,b}	20.7 ± 1.5	4.3 ± 0.9	—
Period $CA_{H0.5}$	31 ± 4	69 ± 18^b	143 ± 12^b	21.7 ± 0.5	4.0 ± 0	29.5 ± 10.2^b
Period $HA_{H0.5}$	26 ± 5	32 ± 7^a	101 ± 17^{a,b}	20.3 ± 0.8	4.0 ± 0.9	—
Period $CA_{H2.0}$	32 ± 6	69 ± 17^b	174 ± 25	20.8 ± 0.8	4.8 ± 0.4	33.8 ± 13.0^b
Period $HA_{H2.0}$	30 ± 7	36 ± 10^a	173 ± 26	20.5 ± 1.1	4.8 ± 0.8	—
Period CA_2	30 ± 7	65 ± 19^b	135 ± 21^b	21.2 ± 1.8	4.7 ± 0.8	34.5 ± 12.1^b
Period HA_2	26 ± 10	33 ± 10^a	87 ± 14^{a,b}	21.7 ± 1.4	4.7 ± 1.0	—

$P\text{aco}_2$, pulmonary arterial $P\text{o}_2$; $P\text{vo}_2$, pulmonary venous $P\text{o}_2$; $\dot{Q}_L$, lobar flow; Pa, pulmonary arterial pressure; Pv, pulmonary venous pressure; Q_{VA}/Q_T, venous admixture.

By analysis of variance $P\text{vo}_2$, Q_{VA}/Q_T, and $\dot{Q}_L$ demonstrated significant differences between ventilatory periods.

[a] Significant difference between control and matched hypoxic period ($P < 0.05$).

[b] Significant decrease from the initial periods C or H and subsequent control or hypoxic periods, respectively ($P < 0.05$).

Note that values of $\dot{Q}_L$ are similar only among period C, period $CA_{H2.0}$, and period $HA_{H2.0}$.

(Q_{VA}/Q_T) showed a trend for values to increase during periods $CA_{H0.5}$ and $CA_{H2.0}$, with values increasing to 168% ± 91% and 168% ± 65%, respectively, of the value during period CA_1. Even when ventilation with halothane was discontinued (period CA_2), Q_{VA}/Q_T remained increased over values calculated during period CA_1 (195% ± 115% of the value during period CA_1). There were no significant differences in mean values of Pa and Pv between periods. The lobar flow ($\dot{Q}_L$) was significantly lower during all hypoxic ventilatory periods than during the control ventilatory periods except during ventilation with 2.0% halothane (period $HA_{H2.0}$). Values of $\dot{Q}_L$ significantly decreased from period C to period CA_1. They remained lower during period $CA_{H0.5}$, increased during period $CA_{H2.0}$, and then decreased again during period CA_2.

Table 3 illustrates the values of pulmonary vascular resistance and its subdivisions during the 10 ventilatory periods. Both R_{tot} and Rm were significantly greater during the hypoxic periods compared with their matched control periods (periods C and H; CA_1 and HA_1; $CA_{H0.5}$ and $HA_{H0.5}$; CA_2 and HA_2), except when comparing period $CA_{H2.0}$ with period $HA_{H2.0}$. During ventilation with 2.0% halothane, R_{tot} and Rm were similar with both control and hypoxic gas ventilation ($P > 0.05$). Values of R_{tot} and Rm followed the same pattern as values of $\dot{Q}_L$. Values of R_{tot} and Rm increased from period C to periods CA_1, $CA_{H0.5}$, and CA_2 ($P < 0.05$). Values of R_{tot} and Rm were similar in periods C and $CA_{H2.0}$. During periods HA_1 and HA_2, both R_{tot} and Rm were significantly greater than during period H. During period $HA_{H0.5}$, both R_{tot} and Rm were similar to values during period H. With the increasing concentration of halothane during period $HA_{H2.0}$, values of both

Table 3. Pulmonary Vascular Resistance and Its Subdivisions During the Ten Ventilatory Periods

	R_{tot}	Ra	Rm	Rv
Period C	0.083 ± 0.01	0.031 ± 0.003	0.016 ± 0.007	0.036 ± 0.007
Period H	0.135 ± 0.007^{a}	0.033 ± 0.021	0.06 ± 0.007^{a}	0.041 ± 0.022
Period CA_1	0.125 ± 0.017^{b}	0.032 ± 0.009	0.046 ± 0.014^{b}	0.047 ± 0.011
Period HA_1	$0.178 \pm 0.036^{a,b}$	0.032 ± 0.015	$0.084 \pm 0.02^{a,b}$	0.063 ± 0.024
Period $CA_{H0.5}$	0.110 ± 0.011^{b}	0.029 ± 0.006	0.036 ± 0.004^{b}	0.045 ± 0.009
Period $HA_{H0.5}$	0.166 ± 0.033^{a}	0.029 ± 0.010	0.074 ± 0.029^{a}	0.063 ± 0.015
Period $CA_{H2.0}$	0.094 ± 0.019^{c}	0.030 ± 0.007	0.022 ± 0.007^{c}	0.043 ± 0.015
Period $HA_{H2.0}$	0.093 ± 0.018^{c}	0.030 ± 0.007	0.022 ± 0.006^{c}	0.041 ± 0.016
Period CA_2	0.125 ± 0.022^{b}	0.031 ± 0.068	0.035 ± 0.005^{b}	0.059 ± 0.02^{b}
Period HA_2	$0.201 \pm 0.04^{a,b}$	0.026 ± 0.009	$0.093 \pm 0.026^{a,b}$	0.082 ± 0.025^{b}

R_{tot}, total resistance; Ra, arterial segment resistance; Rm, middle segment resistance; Rv, venous segment resistance.

All resistance values are measured in units of cm $H_2O \cdot mL^{-1} \cdot min^{-1}$. Explanation of the ventilatory periods can be found within the text.

[a] Significant increase between control periods and matched hypoxic periods ($P < 0.05$).

[b] Significant increase from the initial periods C or H and subsequent control or hypoxic periods, respectively ($P < 0.05$).

[c] Significant decrease between periods CA_1 and $CA_{H2.0}$ ($p < 0.05$) and between periods HA_1 and $HA_{H2.0}$ ($P < 0.05$).

R_{tot} and Rm were further reduced compared with values obtained during period $HA_{H0.5}$. Values of Ra were similar in all 10 ventilatory periods. Values of Rv were also similar in periods C and H. After the production of atelectasis, Rv tended to be higher during the hypoxic periods than in matched control periods, but this difference was not statistically significant ($P > 0.05$). Values of Rv were significantly higher during periods CA_2 and HA_2 than during periods C and H.

Discussion

Hypoxic Pulmonary Vasoconstriction

Previous studies examining the effects of halothane on hypoxic pulmonary vasoconstriction have yielded conflicting results (10–13,22–25). Marshall and Marshall (10) have proposed that halothane might directly inhibit hypoxic pulmonary vasoconstriction but that secondary effects of halothane might indirectly augment hypoxic pulmonary vasoconstriction. The dual effects of halothane might then account for some of the differences in results between groups of investigators. The isolated canine lobe allows for careful control and measurement of these potentially confounding variables (9). In our study we controlled both pulmonary artery Po_2 and vascular pressures in order to eliminate their independent effect on pulmonary vascular resistance. Using an isolated lobe also removes any secondary neuronal and systemic humoral influences and allows the specific effects of halothane on pulmonary vascular resistance to be evaluated.

We used methodology similar to that described by Hakim et al. (15) to subdivide pulmonary vascular resistance into arterial, middle, and venous segment resistances. We have previously described how our experimental preparation allows comparison of our results with those obtained by others despite some methodological differences among the studies (14, 26). In our previous experiments we found that 0.5% halothane prevented the increases in middle segment resistance induced by hypoxia (14). In the normal canine vasculature, we found that both halothane and hypoxia acted solely on the middle vascular segment but had opposing actions; i.e., hypoxia increased Rm whereas halothane decreased Rm. We extended our earlier experiments concerning the interactions of halothane with hypoxia to include the role of prostaglandins by inducing cyclooxygenase blockade (26). Cyclooxygenase blockade acts to decrease the release of vasodilating prostaglandins (e.g., PGI_2), which are released with a hypoxic stimulus and thereby can augment hypoxic pulmonary vasoconstriction (27). We found that after cyclooxygenase inhibition, the middle segment resistance response to hypoxia was greatly augmented. We also found that ventilation with high concentrations of halothane (2.0%), but not with low concentrations of halothane (0.5%), could prevent the increase in middle segment resistance seen in this setting (26). These results suggest that as the intensity of the stimulus for hypoxic pulmonary vasoconstriction is augmented, a greater concentration of halothane is necessary to antagonize the mediators of hypoxic pulmonary vasoconstriction and thereby to block further increases in resistance. In our current experiments we speculated that halothane would be a less potent inhibitor of hypoxic pulmonary vasoconstriction when the hypoxic pressor effect was augmented in an atelectatic isolated lobe compared with the untreated, otherwise normal, isolated lobe.

Experimental Conditions

We attempted to control variables that might independently affect vascular resistance and thereby confound interpretation of our results. We maintained the lobe vasculature in zone 3 conditions for flow during all vascular occlusions by fixing the arterial inflow and venous outflow pressures throughout all ventilatory periods. Also, because hematocrit can independently affect middle segment resistance (28), we maintained hematocrits at similar levels throughout between all periods. Arterial pH and venous pH were allowed to remain in an acidotic range to potentially further augment hypoxic pulmonary vasoconstriction (29). However, both pH and P_{CO_2} were maintained at similar values throughout all the experimental periods and therefore cannot account for any of the differences we observed between periods. Inspired halothane concentrations were also similar between the matched control and hypoxic ventilation periods; i.e., FIHal in period $CA_{H0.5}$ was similar to that in period $HA_{H0.5}$, and FIHal in period $CA_{H2.0}$ was similar to that in period $HA_{H2.0}$. We maintained pulmonary arterial oxygen concentrations at similar levels in all ventilatory periods by setting the level of Pa_{O_2} using a bubble deoxygenator. In this manner the stimulus due to pulmonary arterial oxygen concentrations would be similar between periods and would not independently influence resistance. Mean values of pulmonary venous oxygenation were maintained near 30 mm Hg during all hypoxic ventilatory periods. Any differences between control and hypoxic ventilation periods would have been due to the differences in inspired oxygen concentrations and its effects on pulmonary vascular resistance. Similarly, any differences between periods measured during ventilation with the same F_{IO_2} would have been due to the effects of atelectasis. Lobar venous P_{O_2} started at 115 ± 20 mm Hg during the baseline control period. We had prospectively decided to induce sufficient atelectasis to decrease lobar venous P_{O_2} by approximately 20 mm Hg.

Sublobar Atelectasis

Using a multiple inert gas method, Lee et al. (16) have shown that introduction of steel balls of 4.8-mm diameter into the lower and middle lobes of dogs produces a bimodal pattern of V/Q distribution. They found increased low V/Q regions after atelectasis and suggested that ball bearings of 4.8-mm diameter occlude the airway at a location sufficiently proximal to minimize the effects of collateral ventilation in helping match ventilation and perfusion. They also found a small increase in intrapulmonary shunt, on the order of 14%, in the animals after atelectasis. Therefore, introducing small beads into the airway can produce both increased intrapulmonary shunt and increased V/Q heterogeneity. We used a modification of this model of sublobar atelectasis to mimic the common clinical situation of patchy atelectasis encountered both during anesthesia (1) and in the postoperative period. In our experiments we used similarly sized ball bearings to induce atelectasis and therefore expected that we would produce a similar lesion. We noted that after introducing only 20–30 ball bearings, pulmonary venous P_{O_2} could be decreased by at least 20 mm Hg and venous admixture significantly increased. With this degree of airway obstruction, peak airway pressures increased. Tidal volume was adjusted to maintain similar peak airway pressures to that of the initial control ventilatory period. In this manner, we hoped to minimize the effects of transmitted airway pressure on pulmonary vascular resistance (30–32).

After production of atelectasis (period CA_1), both R_{tot} and Rm increased above levels in the baseline control ventilatory period (period C). When the atelectatic lung was ventilated with a hypoxic gas mixture (period HA_1), both R_{tot} and Rm were further increased compared with the increases induced by atelectasis alone. These values were also higher than those observed due to hypoxia alone (period H). If mean values for total resistance during the baseline periods are compared (period C and period H), the hypoxic stimulus increased resistance by 0.052 cm $H_2O \cdot mL^{-1} \cdot min^{-1}$. A similar hypoxic stimulus after induction of atelectasis (period CA_1 and period HA_1) caused resistance to increase by 0.053 cm $H_2O \cdot mL^{-1} \cdot min^{-1}$. The changes in middle segment resistance follow an almost identical pattern and suggest that both hypoxic ventilation and atelectasis have additive effects at the level of the middle vascular segment. Neither Ra nor Rv showed significant increases during these same periods. These results suggest that atelectasis and lobar hypoxic ventilation have independent but additive effects. As more than 70% of the increased vascular resistance was localized to the middle segment, both lobar hypoxia and sublobar atelectasis stimulate hypoxic pulmonary vasoconstriction. Alternatively, local trauma induced by airway occlusion with ball bearings might increase vascular resistance by release of vasoactive mediators

(16). These mediators, however, have not been shown to have a major influence on middle segment resistance (15).

Inhalation Anesthetics

We previously noted that in the otherwise normal isolated lobe, 0.5% halothane inhibited the specific effects of hypoxia on middle segment resistance (14). In these current studies we found that in the atelectatic lobe, 0.5% halothane no longer fully prevents the increase in Rm and R_{tot} seen with hypoxic pulmonary vasoconstriction, but it does act to diminish the magnitude of the pressor response. These current studies are not completely analogous to our former investigations, as the pulmonary artery concentration of halothane was probably reduced after deoxygenating the pulmonary venous outflow blood. Although we did not measure blood halothane concentrations, the inhibition of hypoxic pulmonary vasoconstriction by pulmonary artery halothane is less than half as potent as the inhibition caused by alveolar halothane. Thus it is unlikely that the absence of pulmonary artery halothane is the predominant mechanism through which 0.5% halothane has a diminished effect in the atelectatic lobe. An increased concentration of halothane (2.0%) fully prevented the increase in Rm and R_{tot} during ventilation with either control or hypoxic gas mixtures (periods $CA_{H2.0}$ and $HA_{H2.0}$). The effects of halothane on resistance were reversible because both R_{tot} and Rm increased during periods CA_2 and HA_2 when the lobes were ventilated without halothane.

The interaction of halothane with gas exchange homeostasis is less clear than the effects on pulmonary vascular resistance. As expected, Q_{VA}/Q_T increased, and pulmonary venous oxygenation decreased, after the production of sublobar atelectasis. Although both Q_{VA}/Q_T and pulmonary venous oxygenation tended to worsen during halothane ventilation, these changes did not achieve statistical significance. Also, Q_{VA}/Q_T tended to worsen spontaneously from the initial measurements during period CA_1 to the final measurements during period CA_2, thus obscuring further the independent effects of ventilation with halothane on Q_{VA}/Q_T. During periods $CA_{H0.5}$ and $CA_{H2.0}$, there was a trend for the animals with the larger values of venous admixture to have the lesser increases after halothane administration. We did not directly measure oxygen saturations or blood contents of oxygen but rather calculated contents from the measured values of Po_2. We found very small differences between lobar venous and lobar arterial Po_2 during all the hypoxic periods, and this did not allow for meaningful shunt calculations. Therefore, no attempt was made to calculate values of Q_{VA}/Q_T during the hypoxic ventilatory periods. We could not therefore determine if the animals with the strongest response to hypoxia had the larger increases in venous admixture in response to halothane administration.

If hypoxic vasoconstriction acts to minimize Q_{VA}/Q_T, we would expect that as middle segment resistance increased, Q_{VA}/Q_T would decrease. We therefore compared the change in Q_{VA}/Q_T with the change in middle segment resistance in each animal. We calculated the change in Q_{VA}/Q_T from each control ventilation period to the subsequent control ventilation period (e.g., period C to period CA_1; period CA_1 to period $CA_{H0.5}$; period $CA_{H0.5}$ to period $CA_{H2.0}$; period $CA_{H2.0}$ to period CA_2). We then similarly calculated the change in middle segment resistance and then compared the change in middle segment resistance with the change in Q_{VA}/Q_T using linear regression. We found a correlation coefficient of 0.33 ($P > 0.05$) for the resultant relationship. Using the same methods, we also compared the change in total resistance with the change in Q_{VA}/Q_T and found a correlation coefficient of 0.3 ($P > 0.05$). This suggests that changes in resistance were not associated with concurrent changes in Q_{VA}/Q_T. This was different from prior observations in canine atelectasis, in which systemic administration of a vasodilating prostaglandin caused increased shunt and the largest increases in shunt occurred in the animals with the strongest hypoxic vasoconstriction (17,33). In a canine model of one-lung atelectasis, nitroprusside administration was also associated with large increases in shunt (34). Our data suggest that halothane administered by inhalation may act differently than vasodilators administered systemically. If alveoli receive any ventilation, then some halothane would enter these alveoli and cause vasodilation. In alveoli that receive no ventilation (true intrapulmonary shunt), the only halothane that would reach the blood vessels would have to arrive through the circulation. In our preparation, blood passed through a deoxygenator before perfusing the lobar vasculature. It is likely that significant quantities of halothane were also removed along with oxygen. This would tend to amplify the inhalational effect of halothane because the vascular delivery was probably low. Then halothane would vasodilate those lung units with low V/Q ratios to a greater extent than units with true shunt. This would cause a lesser increase in Q_{VA}/Q_T than if both low V/Q and true shunt units were equally vasodilated. The vasodilator effects of halothane might be limited in the most severely affected lung regions and thus prevent worsening of shunt. Furthermore, comparisons of Q_{VA}/Q_T between periods were obscured by the ongoing increases in Q_{VA}/Q_T with time in our preparation (i.e., there were large increases in Q_{VA}/Q_T from period CA_1 to period CA_2). This variability does not allow for a more complete evaluation of the interactions of halothane with gas exchange homeostasis.

We conclude that halothane at low concentrations (0.5%) acts initially to diminish the additive increases in pulmonary vascular resistance with hypoxic ventilation (lobar hypoxia) and atelectasis (sublobar hypoxia). Increasing halothane concentrations (2.0%) may prevent the increases in pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction whether induced by lobar hypoxia or sublobar atelectasis. This would be consistent with the hypothesis that sublobar atelectasis results in increased pulmonary vascular resistance through augmentation of hypoxic pulmonary vasoconstriction and not by mechanical compression of the pulmonary vessels. Our current findings are similar to our previous observations of the interaction of halothane with cyclooxygenase inhibition (26). It is possible to minimize the effects of low concentrations of halothane by increasing the strength of the hypoxic pressor response (cyclooxygenase blockade), or, as these results suggest, if hypoxic pulmonary vasoconstriction is required to maintain adequacy of gas exchange, then increasing concentrations of halothane may interfere with these homeostatic mechanisms.

Although our findings may not be directly applicable to the clinical setting, we caution that high concentrations of halothane do interfere directly with hypoxic pulmonary vasoconstriction and may be a cause of worsened gas exchange when underlying lung disease is present. As well, when evaluating studies examining the effects of halothane on hypoxic pulmonary vasoconstriction, the method by which alveolar hypoxia is produced and the route(s) by which halothane is administered may be contributing factors to the observed results.

The authors thank T. Ekersley and Mrs. K. Brown for their technical and secretarial assistance.

References

1. Nunn JF. Applied respiratory physiology. 3rd ed. Chapter 9. Respiratory aspects of anesthesia. London: Butterworth & Co. 1987:350–91.
2. Rehder K, Knopp TJ, Sessler AD, Didier EP. Ventilation-perfusion relationship in young healthy awake and anesthetized-paralyzed man. J Appl Physiol 1979;47:745–53.
3. Bindslev L, Hedenstierna G, Santesson J, Gottlieb I, Carvallhas A. Ventilation-perfusion distribution during inhalation anaesthesia. Acta Anaesthesiol Scand 1981;25:360–71.
4. Dueck R, Young I, Clausen J, Wagner PD. Altered distribution of pulmonary ventilation and blood flow following induction of inhalation anesthesia. Anesthesiology 1980;52:113–25.
5. Defarer JG, Lundin G, Arborelius M. Effect of unilateral hypoxia in pulmonary blood flow distribution in normal subjects. J Appl Physiol 1960;15:169–74.
6. Kirilloff LH, Owens GR, Rogers RM, Mazzocca MC. Does chest physical therapy work? Chest 1985;88:435–44.
7. Benumof JL. Mechanism of decreased blood flow to atelectatic lung. J Appl Physiol 1979;46:1047–8.
8. Domino KB, Wetstein L, Glasser SA, et al. Influence of mixed venous oxygen tension (Pv_{O_2}) on blood flow to atelectatic lung. Anesthesiology 1983;59:428–34.
9. Miller FL, Chen L, Malmkvist G, Marshall C, Marshall BE. Mechanical factors do not influence blood flow distribution in atelectasis. Anesthesiology 1989;70:481–8.
10. Marshall BK, Marshall C. Anesthesia and pulmonary circulation. In: Covino B, Fozzard H, Rehder K, Strichmat Z, eds. Effects of anesthesia. Bethesda: American Physiology Society, 1985.
11. Mathers J, Benumof JL, Wahrenbrock EA. General anesthetics and regional hypoxic pulmonary vasoconstriction. Anesthesiology 1977;46:111–4.
12. Marshall C, Kim SD, Marshall BE. The actions of halothane, ibuprofen and BW755C on hypoxic pulmonary vasoconstriction. Anesthesiology 1987;66:537–42.
13. Bjertnaes LJ. Hypoxia induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalation anaesthetics. Acta Anaesthesiol Scand 1977;21:133–47.
14. Johnson D, Mayers I, To T. The effects of halothane in hypoxic pulmonary vasoconstriction. Anesthesiology 1990;72:125–33.
15. Hakim TS, Michel RP, Chang HK. Partitioning of pulmonary vascular resistance in dogs by arterial and venous occlusion. J Appl Physiol 1982;52:710–5.
16. Lee L, Ueno O, Wagner PD, West JB. Pulmonary gas exchange after multiple airway occlusion by beads in the dog. Am Rev Respir Dis 1989;140:1216–21.
17. Thomas HM, Garrett RC. Strength of hypoxic vasoconstriction determines shunt fraction in dogs with atelectasis. J Appl Physiol 1983;53:44–51.
18. Marshall BE, Marshall C, Benumof J, Saidman LJ. Hypoxic pulmonary vasoconstriction in dogs: effects of lung segment size on oxygen tension. J Appl Physiol 1981;51:1543–51.
19. Rossing RG, Cain SM. A nomogram relating Po_2, pH, temperature and hemoglobin saturation in the dog. J Appl Physiol 1966;21:195–201.
20. Burnett RW, Noonan DC. Calculations and correction factors used in determination of blood pH and blood gases. Clin Chem 1974;20:1499–506.
21. Sokol RR, Rohlf FJ. Biometry. Statistical tables. San Francisco: WH Freeman, 1981:81.
22. Loh L, Sykes MK, Chakrabarti MK. The effects of halothane and ether on the pulmonary circulation in the innervated perfused cat lung. Br J Anaesth 1977;49:309–13.
23. Bjertnaes L. Intravenous versus inhalation anesthesia. Acta Anaesth Scand 1982;75:18–24.
24. Sykes MK, Gibbs JM, Loh L, Marin JBL, Obdrzalek J, Arnot RN. Preservation of the pulmonary vasoconstrictor response to alveolar hypoxia during administration of halothane to dogs. Br J Anaesth 1978;50:1185–96.

25. Benumof JL, Alfery DD. Anesthesia for thoracic surgery. In Miller R, ed. Anesthesia. 2nd ed. New York: Churchill Livingstone, 1986:1385.
26. Johnson D, Mayers I, Hurst T. Halothane inhibits hypoxic pulmonary vasoconstriction in the presence of cyclooxygenase blockade. Can Anaesth Soc J 1990;37:287–95.
27. Voelkel NF, Gerber JG, McMurtry IF, Nies AS, Reeves JT. Release of vasodilator prostaglandin, PGI_2, from isolated rat lung during vasoconstriction. Circ Res 1981;48:207–13.
28. Julien M, Hakim TS, Vahi R, Chang HK. Effect of hematocrit on vascular pressure profile in dog lungs. J Appl Physiol 1985;58:743–8.
29. Rudolph AM, Yuan S. Response of the pulmonary vasculature to hypoxic and H^+ ion concentration. J Clin Invest 1966;45:399–411.
30. Niden AH. The acute effects of atelectasis on the pulmonary circulation. J Clin Invest 1965;43:810–24.
31. Quebbeman EJ, Dawson CA. Influence of inflation and atelectasis on the hypoxic pressor response in isolated dog lung lobes. Cardiovasc Res 1976;10:672–7.
32. Pirlo AF, Benumof JL, Trousdale FR. Atelectatic lobe blood flow: open vs. closed chest, positive pressure vs. spontaneous ventilation. J Appl Physiol 1981;50:1022–6.
33. Garrett RC, Thomas HM III. Relation of prostanoids to strength of hypoxic vasoconstriction in dogs with lobar atelectasis. J Appl Physiol 1985;59:72–7.
34. Colley PS, Cheney FW. Sodium nitroprusside increases Qs/Qt in dogs with regional atelectasis. Anesthesiology 1977;47:338–41.

Is Caffeine Withdrawal the Mechanism of Postoperative Headache?

M. Fennelly, FFARCSI, MRCPI, D. C. Galletly, MB, ChB, FFARACS, FFARCS, and G. I. Purdie, BSc

FENNELLY M, GALLETLY DC, PURDIE GI. Is caffeine withdrawal the mechanism of postoperative headache? Anesth Analg 1991;72:449–53.

This study examined the hypothesis that headache after general anesthesia is related to a caffeine withdrawal state. Two hundred eighty-seven patients undergoing minor elective procedures under general anesthesia were studied. Four to six hours after anesthesia each patient completed a questionnaire assessing his or her own alcohol, tobacco, and caffeine consumption, and the occurrence of postoperative side effects. A highly significant difference was found between the caffeine consumption of patients with and without preoperative ($P = 0.0035$) and postoperative ($P < 0.0001$) headache. Logistic regression analysis of trend between headache and caffeine consumption suggested that with each 100-mg increase in caffeine consumption, there was a 12% increase in the odds of headache developing in the immediate preoperative period ($P < 0.0066$) and a 16% increase in the odds of postoperative headache developing ($P < 0.0001$). No relationship was found between headache and the patients' age, sex, usual frequency of headache, consumption of alcohol or nicotine, or the anesthetic agents or adjuvants used. It is concluded that postoperative headache is related to caffeine intake and that this relationship is explained, at least in part, by a perioperative caffeine withdrawal syndrome.

Key Words: COMPLICATIONS, HEADACHES—postoperative. PHARMACOLOGY, CAFFEINE.

Caffeine is the most widely consumed, stimulatory psychotropic. It is a methyl xanthine, the principal action of which is thought to be brought about by a competitive antagonism of the inhibitory neurotransmitter adenosine (1). Caffeine-related morbidity is relatively common and occurs either as a direct result of caffeine intake or as a result of withdrawal after abstinence (2–8).

Caffeine toxicity, or "caffeinism," is due either to an excessive caffeine intake or to an increased sensitivity to its effects. Described as a syndrome similar to that of anxiety neurosis, it is associated with nervousness, irritability, headache, muscular twitching, insomnia, and myocardial stimulation, which may be reflected in premature ventricular contractions and tachycardia (2–4).

A caffeine withdrawal syndrome has also been described, the most consistent symptom being headache. Withdrawal typically occurs within 24 h of abstinence in those who regularly consume large quantities of caffeine (5–7). Objective (electromyographic alterations) evidence of withdrawal may be detected after only 3 h of abstinence (8).

In North America it has been estimated that more than 90% of adults consume caffeine-containing beverages, with a daily per capita intake averaging approximately 200 mg (9). Because the amount of caffeine associated with withdrawal symptoms may be as low as 190 mg/day, it is possible that a significant proportion of the population could suffer withdrawal if intake is stopped (8).

Before anesthesia, patients routinely undergo periods of fasting similar to those that are capable of precipitating withdrawal. Many patients are high caffeine users (10), and it is therefore to be expected that some will suffer withdrawal symptoms in the perioperative period. One of the most frequent postoperative side effects of general anesthesia is headache (11,12), and, although commonly ascribed to the effect of anesthetic drugs, this symptom could be the result of caffeine abstinence. If this hypothesis were correct, it would be expected that a significant positive relationship would be found between the incidence of postoperative headache and the preoperative ingestion of caffeine. In this survey we examine this relationship.

Received from the Department of Anaesthesia, Royal Postgraduate Medical School, Hammersmith Hospital, London, England; University Section of Anaesthesia, Wellington School of Medicine, Wellington, New Zealand. Accepted for publication November 15, 1990.

Address correspondence to Dr. Galletly, Department of Anaesthesia, Wellington School of Medicine, Wellington, New Zealand.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Methods

This was an open study of 300 male and female patients between the ages of 18 and 75 yr undergoing minor outpatient surgery under general anesthesia, who were not being treated medically with methylxanthine medications. All patients underwent endoscopic or body surface procedures on the morning of study and, in the afternoon, between 4 and 6 h postoperatively, were approached for inclusion in the study. Each patient was asked to complete a questionnaire to ascertain the following (in addition, the questionnaire contained other items unrelated to this present study):

1. The occurrence of specified side effects after anesthesia, up until the time of questionnaire completion. Side effects sought included dizziness, unsteadiness, headache, nausea, vomiting, and irritability using the format:

   At any time *AFTER* your anesthetic today did you have any of the following? (Circle your answer.)
   Nausea: Definitely yes Unsure Definitely no
2. Using a similar format, whether any of these side effects had been present on the day of operation at any time before the anesthesia.
3. On how many days a week alcohol was normally consumed and whether any alcohol had been consumed on the day before anesthesia.
4. The daily number of cigarettes, cigars, pipes, or cups of caffeinated tea, filtered or instant coffee consumed. All questions were of similar format:

   Over the past week how many cups of *instant* coffee would you normally drink each day (do not include special decaffeinated coffee)—circle one only.
   None 1 2 3 4 5 6 7 8 9 10 More than 10
5. Whether the patient had consumed any food or caffeinated tea or coffee before or after the anesthesia up until the time of questionnaire completion.
6. The usual frequency of headaches.
   - (a) Frequently (one or more times each week)
   - (b) Often (one to three times each month)
   - (c) Infrequently (less than once every month)
   - (d) Never
7. Whether the patient had taken any caffeine-containing or non-caffeine-containing analgesic medications two or more times in the previous week. A list of 14 analgesics, commonly prescribed in the United Kingdom, was then given for circling.

To make the sample representative of the normal outpatient population, patient selection was determined solely from operating room schedules, and all patients meeting the entry criteria were included where possible. No attempt was made to influence the course of anesthesia or recovery before completion of the questionnaire. Patients were not told the nature or purpose of the questionnaire before its completion.

The analysis was done as follows. Daily caffeine consumption was calculated in milligrams per day using conversion factors derived from previously published sources (2,13): tea, 50 mg/cup; instant coffee, 90 mg/cup; percolated or filtered coffee, 120 mg/cup.

For parametric analysis, caffeine consumption data were normalized using a power transformation (square root) to reduce the negative skew. Where the mean value is quoted below, this was derived from transformed data.

Categorical data were analyzed using a χ^2 test, and comparisons of mean caffeine consumption were made using Student's t-tests on the transformed caffeine data. Correlations between ordinal data were made using a Spearman rank correlation.

The trend between increasing caffeine intake and proportion of patients with headache was modeled using a logistic regression procedure (SAS) with calculation of odds ratio.

Results

Fully completed data sheets were obtained from 287 patients with a mean age of 40 yr (±14.5 SD) of whom 62 (22%) were male. Sixty-seven percent were premedicated, 34% with a benzodiazepine and 23% with an opioid/anticholinergic. Anesthesia comprised intravenous induction with either propofol (71%) or thiopental (29%), supplemented with fentanyl (48%), nitrous oxide (96%), isoflurane (83%), or halothane (10%).

Caffeinated tea or coffee was consumed by 96% of the patients. The calculated daily intake from these sources ranged from 0 to 2120 mg with a mean of 397 mg. Forty-four percent of the total caffeine intake was made up from tea, 44% from instant coffee, and 12% from filtered coffee. There was no significant relationship between the caffeine intake and the sex, age, type of operation, or anesthetic agents used. Thirty-five (12%) patients had consumed tea or coffee preoperatively, and by the time of completion of the questionnaire, 136 (47.5%) patients had consumed tea or coffee postoperatively.

Table 1 shows the incidence of side effects recalled by patients for the post- and preoperative periods. For each side effect a comparison is made between

Table 1. Incidence of Side Effects That, Postoperatively, Patients Could Recall in the Pre- and Earlier Postoperative Period as a Function of Caffeine Consumption

		Mean caffeine consumption[a]		
Side effect	Incidence (%)	With side effect	No side effect	P
Preoperative period				
Headache	25	490 (416–571)	360 (321–402)	0.0035
Nausea	7	402 (267–564)	387 (350–426)	NS
Vomiting	3	206 (49–470)	397 (360–435)	NS
Dizziness	5	239 (134–374)	392 (355–432)	NS
Unsteadiness	6	369 (238–529)	387 (350–426)	NS
Irritability	7	382 (273–508)	395 (356–435)	NS
Postoperative period				
Headache	43	504 (450–562)	323 (279–371)	<0.0001
Nausea	27	380 (303–465)	400 (358–445)	NS
Vomiting	17	402 (307–509)	391 (352–432)	NS
Dizziness	30	442 (361-530)	362 (323–403)	NS
Unsteadiness	30	422 (347–504)	374 (334–417)	NS
Irritability	7	298 (220–388)	407 (368–447)	NS

NS, not significant.

P = significance level (Student's t-test) between patients reporting side effects and those without side effects.

[a] Ranges given in parentheses are the 95% confidence limits for the mean.

the mean caffeine consumption for those who did and that for those who did not report the side effect. A significantly higher caffeine consumption was found for patients reporting the symptom of headache both for the preoperative and postoperative periods. No significant relationship was observed between perioperative headache and the patients' sex, age, or surgical category, the anesthetic agents or adjuvants used, or previous frequency of headache. The frequency with which patients remembered postoperative nausea and dizziness was statistically greater in patients given an opioid.

Figures 1 and 2 show the frequency of recall for pre- and postoperative headache according to daily caffeine intake. For both periods, the proportion suffering headache increased with increasing consumption. Although the insufficient numbers of patients (nine) available to us meant that we could not be certain as to the effect of total abstinence from caffeine, postoperative headache did not develop in any patient who was an abstainer.

Logistic regression analysis of recalled preoperative headache versus caffeine intake demonstrated a significant trend between the parameters, a trend modeled by the equation

$$\ln (P/1 - P) = [0.0011 \times \text{caffeine (mg)}] - 1.628.$$

Each 100-mg increase in caffeine consumption was associated with a 12% increase in the odds of preoperative headache developing (95% confidence interval, 3%–21%; χ^2, 7.38; $P < 0.0066$).

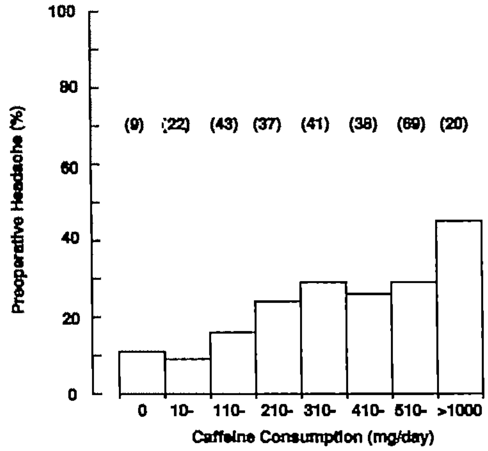


Figure 1. Proportion of patients recalling headache during the preoperative period against daily caffeine consumption. Numbers in parentheses refer to the total numbers of patients within each dose group excluding those who were uncertain as to whether they had suffered a preoperative headache.

For the probability of postoperative headache, the logistic regression equation was

$$\ln (P/1 - P) = [0.0015 \times \text{caffeine (mg)}] - 0.98.$$

Each 100-mg increase in caffeine consumption was associated with a 16% increase in the odds of postoperative headache developing (95% confidence interval, 7%–25%; χ^2, 14.4; $P < 0.0001$).

The number of patients consuming caffeine preoperatively was small (35); however, there was a suggestive negative relationship between preoperative caffeine consumption and preoperative headache

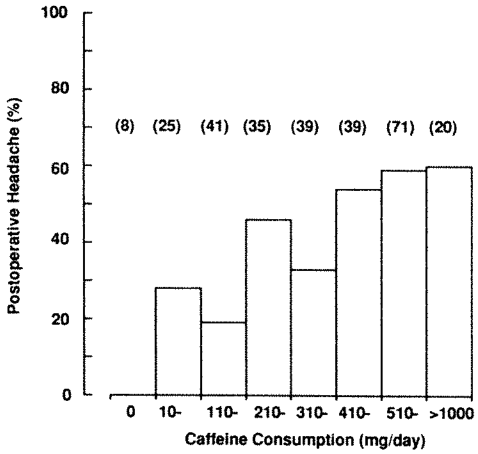


Figure 2. Proportion of patients recalling headache during the postoperative period against daily caffeine consumption. Numbers in parentheses refer to the total numbers of patients within each dose group excluding those who were uncertain as to whether they had suffered a postoperative headache.

($P = 0.07$), although not with postoperative headache.

No patient regularly ingested caffeine- or theophylline-containing medications. No correlation was found between alcohol or tobacco consumption and pre- or postoperative side effects.

Discussion

Minor postoperative morbidity is a common and expected sequelae of general anesthesia. The most frequent side effects attributed to anesthesia include dizziness, weakness, headache, and nausea (14). The reported incidence of headache varies widely, ranging from 13% to 80%. In this study we tested the hypothesis that postoperative morbidity, specifically headache, is related to abstinence from regular daily ingestion of caffeine.

Previous studies examining the effect of caffeine abstinence in subjects with high daily intakes have demonstrated that caffeine withdrawal generally occurs after 13–23 h of abstinence (15). Symptoms of withdrawal include headache, sleepiness, reduced activity, and, in some studies, anxiety, irritability, or gastrointestinal upset. The most consistent and sensitive feature of caffeine withdrawal is headache. These headaches have been relieved by proprietary preparations containing caffeine but not by aspirin alone (5).

In this study we have demonstrated in a group of postoperative patients a significant positive relationship between patient-reported headache and daily caffeine intake. Since presenting our original hypothesis in 1989 (16), other authors have observed consistent findings in volunteer subjects. Thus, Van Dusseldorp and Katan demonstrated that cessation of moderate daily caffeine intake (mean, 435 mg/day) was associated with an increased frequency of headache for a mean of 2.3 days with a range of 1–6 days (17).

Because this survey was an open study of all patients undergoing general anesthesia, we cannot say to what extent the caffeine/headache relationship was influenced by general anesthesia in comparison to unanesthetized patients undergoing abstinence. However, headache was a common symptom recalled for the preoperative period as well as the postoperative period, and this also was most common in those patients with the highest caffeine consumption. Furthermore, the level of caffeine consumed in those patients with and without headache in this present study (500 vs 323 mg) is similar to that reported for psychiatric inpatients (616 vs 395 mg) (5).

In recent reports, caffeine administration has proved to be effective in reducing headache after spinal puncture (18,19). Although the direct action of caffeine could explain the analgesic effect, it is possible that additional effects could be the result of counteracting a caffeine withdrawal owing to reduced oral intake as a result of fasting, pain, and the need to maintain the supine position.

The mean caffeine consumption of patients in this series was 397 mg/day, almost twice that recorded in the North American survey. It has been estimated that in Ontario, 25% of adults consume five or more cups of tea or coffee per day (9). In the present study, 56% of patients consumed this quantity. Thus, although it is difficult to correlate figures accurately it seems probable that the intake for our U.K. sample is considerably greater.

We believe the findings from this study have a number of implications. First, patients with a high preoperative caffeine intake have a high incidence of postoperative headache that may be amenable to prophylactic, preoperative caffeine ingestion. In addition, if specific anesthetic agents are shown to be associated with a high incidence of headache, they can be avoided in the anesthetic management of high caffeine consumers. To our knowledge, however, no previous study has examined the relationship between headache and anesthesia in patients matched for caffeine intake.

Second, caffeine intake and withdrawal may be an important confounding factor in research or clinical investigations using fasting individuals. Although a patient may be asked to abstain from caffeine-containing beverages for only 12–24 h before a study, the withdrawal syndrome may persist for 5 days (15).

Third, international differences may exist in caffeine intake, and therefore studies of minor drug morbidity may not be entirely comparable between different geographic areas.

Finally, although we have specifically examined the symptom of headache, one might wonder what else might be involved in the caffeine-withdrawal state. Because of the known effects of methylxanthines on myocardium and vascular as well as bronchial smooth muscle, it is possible that patients with neurosurgical, cardiac, or bronchospastic conditions may have clinically significant physiological alterations during withdrawal.

Two other findings of this study are also worthy of comment. Surprisingly, we found that approximately 12% of patients consumed caffeinated beverages on the morning of surgery despite being instructed to fast. Also, a considerable number of patients reported symptoms of morbidity in the pre- as well as the postoperative period. Thus, in any assessment of drug morbidity, a patient should be assessed before drug ingestion as well as after. This seems particularly so with regard to headache.

The results of this study suggest that headache after general anesthesia is related to preoperative caffeine withdrawal consequent upon moderate daily levels of caffeine intake.

References

1. Rall TW. Evolution of the mechanism of action of methylxanthines: from calcium mobilisers to antagonists of adenosine receptors. Pharmacologist 1982;24:274–87.
2. Editorial. Coffee, should we stop drinking it? Lancet 1981;i:256.
3. Greden JF. Anxiety or caffeinism: a diagnostic dilemma. Am J Psychiatry 1974;131:963–6.
4. Bruce MS, Lader M. Caffeine abstention in the management of anxiety disorders. Psychol Med 1989;19:211–4.
5. Greden JF, Victor BS, Fontaine P, Lubetsky M. Caffeine withdrawal headache: a clinical profile. Psychosomatics 1980;21:411–8.
6. Stringer KA, Watson WA. Caffeine withdrawal symptoms. Am J Emerg Med 1987;5:469.
7. Smith R. Caffeine withdrawal headache. J Clin Pharmacol Ther 1987;1:53–7.
8. White BC, Lincoln CA, Pearce NW, Reeb R, Vaida C. Anxiety and muscle tension as a consequence of caffeine withdrawal. Science 1980;209:1547–8.
9. Gilbert RM, Marshman JA, Schwieder M, Berg R. Caffeine content of beverages as consumed. Can Med Assoc J 1976;114:205–7.
10. Smith J, Pearson S, Marks V. Plasma caffeine concentrations in outpatients. Lancet 1982;ii:985–6.
11. Ogg TW. An assessment of post-operative outpatient cases. Br Med J 1974;4:573–6.
12. Fahy A, Marshall M. Postanaesthetic morbidity in outpatients. Br J Anaesth 1969;41:433–8.
13. Rall TW. Central nervous system stimulants. In: Gilman AG, Goodman L, Rall TW, Murad F, eds. The pharmacological basis of therapeutics, 7th ed. New York: Macmillan Publishing, 1985:589–603.
14. Moss E, Hooper MB. Morbidity following day case anaesthesia. In: Hindmarsh I, Jones JG, Moss E, eds. Aspects of recovery from anaesthesia. Chichester: Wiley, 1987:17–25.
15. Griffiths RR, Bigelow GE, Liebson IA. Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. J Pharmacol Exp Ther 1986;230:416–25.
16. Galletly DC, Fennelly M, Whitwam JG. Does caffeine withdrawal contribute to postanaesthetic morbidity? Lancet 1989;i:1335.
17. Van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. Br Med J 1990;300:1558–9.
18. Jarvis AP, Greenwalt JW, Fagraeus L. Intravenous caffeine for postdural puncture headache. Anesth Analg 1986;65:316–7.
19. Baumgarten RK. Should caffeine become the first line treatment for postdural puncture headache? Anesth Analg 1987;66:913–4.

Halothane 1.5 MAC, Isoflurane 1.5 MAC, and the Contractile Responses of Coronary Arteries Obtained From Human Hearts

E. Villeneuve, MD, G. Blaise, MD, J. C. Sill, MD, M. J. Guerard, MD, J. Buluran, BSc, and D. Girard, MD

VILLENEUVE E, BLAISE G, SILL JC, GUERARD MJ, BULURAN J, GIRARD D. Halothane 1.5 MAC, isoflurane 1.5 MAC, and the contractile responses of coronary arteries obtained from human hearts. Anesth Analg 1991; 72:454–61.

Active vasoconstriction of epicardial coronary arteries can cause myocardial ischemia in patients with coronary artery disease. Relief of vasoconstriction can improve blood flow to the heart. The purpose of this study was to determine if 1.5 MAC halothane and 1.5 MAC isoflurane would each attenuate contractions evoked by three putative mediators of coronary constriction in coronary arteries removed from the hearts of human beings. Hearts were obtained in the operating room from five patients undergoing cardiac transplantation and from six brain-dead patients undergoing organ donation procedures. Coronary arteries were dissected free, cut into rings, and studied in organ chambers. Endothelium-dependent relaxations to 10^{-6}M bradykinin were examined; they indicated a variable degree of endothelial dysfunction in vessels used in the experiments. Contractile responses to 40 mM KCl were tested and were used as control contractions. Contractions evoked by serotonin, histamine, and prostaglandin $F_{2\alpha}$ were measured and were expressed as a percent of contractile responses evoked by 40 mM KCl. Halothane depressed the agonist-induced contractions. Maximal contractile responses to serotonin were 130% ± 28% in untreated rings and 63% ± 10% in rings exposed to halothane ($P < 0.03$). Responses to histamine were 183% ± 46% untreated and 121% ± 26% during halothane administration ($P < 0.05$), and responses to prostaglandin $F_{2\alpha}$ were 227% ± 42% untreated and 148% ± 18% with halothane ($P < 0.05$). Isoflurane had no effect on contractions. The results demonstrate that 1.5 MAC halothane, but not 1.5 MAC isoflurane, attenuates contractile responses evoked by putative mediators of coronary vasoconstriction in coronary arteries removed from the hearts of human beings.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. HEART, CORONARY OCCLUSION AND CONTRACTILITY.

Active vasoconstriction of proximal coronary arteries may cause or worsen exertional angina, may precipitate unstable angina, and may be responsible for silent ischemia (1–6). The role of coronary vasoconstriction in myocardial infarction is less understood, but powerful constrictor agonists are released during coronary thrombosis and the ensuing constriction may sustain a thrombotic process and contribute to infarction (7). Proximal coronary artery dilators are beneficial in both acute and chronic coronary syndromes (5–7). Halothane and isoflurane are vasodilators. Both attenuate contractile responses of dog and pig coronary arteries in both ex vivo and in vivo studies (8–10). However, their effects on human coronary arteries are unknown. The purpose of this investigation was to determine if 1.5 MAC halothane and 1.5 MAC isoflurane inhibit contractions evoked by three putative mediators of coronary constriction in coronary arteries removed from the hearts of human beings.

The causes of proximal coronary artery constriction are not known (11). Serotonin (2,7), prostaglandins (7), and histamine (12,13) have been associated with coronary vasoconstriction in patients with preexisting coronary artery disease. Therefore, they were used to evoke contractions in the current experiment. Serotonin is released by platelets when activated by atherosclerotic coronary artery plaques (14,15) and during platelet aggregation and coronary

---

Supported in part by grants from the Canadian Heart Foundation 871167, Medical Research Council of Canada MA10044 (G.B.) and grant HL 38668 (NIH) (J.C.S.).

Received from the Departments of Anesthesiology and Pathology, Université de Montréal, Montreal, Quebec, Canada; and the Mayo Clinic, Rochester, Minnesota. Accepted for publication November 19, 1990.

Address correspondence to Dr. Blaise, Department D'Anaesthesia, Hopital Notre Dame, Sherbrooke Street East, Case Postale 1560, Montreal, Quebec H2L 4K8, Canada.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

thrombosis (7). Histamine is a constrictor released by mast cells. Mast cells are increased in the adventitia of atherosclerotic coronary arteries during coronary thrombosis, suggesting that endogenous histamine may be an important cause of localized coronary constriction (12,16). All three agonists have been shown to contract isolated human coronary arteries (17–19).

Prevention of coronary artery constriction and preservation of blood flow to the heart is a goal in managing patients with coronary artery disease (6). Whether or not halothane and isoflurane attenuate contractions of human coronary arteries may, therefore, have clinical implications.

Methods

The purpose of the study was to determine if 1.5 MAC halothane and 1.5 MAC isoflurane each attenuated the contractile response in isolated human coronary arteries evoked by serotonin, histamine, and prostaglandin $F_{2\alpha}$. The protocol was approved by the Institutional Review Board, and informed consent was obtained from living patients or from the relatives of deceased patients. Five hearts were obtained from patients with heart failure who were undergoing cardiac transplantation. Six hearts were obtained from brain-dead patients who were undergoing surgery for removal of kidneys and other organs for donation purposes. (Hearts from brain-dead patients were available for laboratory studies rather than for donation due to the presence of cardiac or coronary artery disease.) Description of the patients is provided in Table 1.

Hearts were removed in the operating room and immersed in aerated (95% O_2–5% CO_2) Krebs-Ringer solution at 4°C, pH 7.40–7.49, with the following composition (in mM): NaCl 119, KCl 4.8, $CaCl_2$ 2.6, $MgSO_4$ 1.2, KH_2PO_4 1.2, and glucose 4. The hearts were immediately transferred to the laboratory, where the coronary arteries were dissected free, cleaned of surrounding fat and connective tissue, and cut into rings 5 mm long. Special care was taken to avoid touching the endothelium-lined luminal surface. The rings were suspended in organ chambers each containing 25 mL aerated Krebs-Ringer solution at 37°C. The rings were attached to strain gauges (Harvard #52-9503), and isometric tension was recorded (Hewlett Packard amplifier 8802A and Gould 480 recorder).

Eleven hearts were studied. Four provided vessels for the halothane studies, and four provided vessels for the isoflurane studies. Vessels from three hearts were used for both halothane and isoflurane studies. Each heart provided five or six pairs of rings. Rings from the same vessel of the same heart were studied in pairs in tandem, one ring was treated with a volatile anesthetic whereas the other was untreated and served as a control. Rings were exposed to a single contractile agonist, either serotonin, histamine, or prostaglandin $F_{2\alpha}$. Each agonist was investigated using eight to 10 pairs of rings removed from seven hearts.

The optimal point on the length-tension curve was determined in each ring by varying passive tension between 10 and 16 g and determining the passive tension that resulted in the greatest contractile response to 20 mM KCl. Each ring was then maintained at its optimal passive tension throughout the experiment. The maximum tension that developed after a standard 40 mM KCl challenge was recorded, and this response was used as a reference. Contractile and relaxation responses during the experiment were compared with this reference contraction.

Presence or absence of endothelial function was tested in all rings by observing the relaxation response of rings precontracted with 20 mM KCl to a single 10^{-6} M dose of bradykinin. (Bradykinin is a useful test for endothelial function. In arteries from many species, including those from humans, it causes vascular smooth muscle relaxation by evoking release of relaxing factors from the endothelium [17,20].)

Isoflurane and halothane were delivered by vaporizers (Fluotec-Fraser Sweatman, Isotec-Ohmeda BOC), and the concentration of the anesthetics in the gas entering each chamber was adjusted to 1.5 MAC (1.1% halothane, 1.7% isoflurane) (21) using a calibrated gas analyzer (Siemens Servo gas monitor 120). Concentrations of anesthetics in the chamber fluid were monitored by removing 2-mL aliquots of Krebs-Ringer solution, extracting the anesthetic in hexane, and measuring the concentrations using gas chromatography with electron capture (Hewlett Packard 1700C).

Isoflurane and halothane were administered for 60 min to measure effects of the anesthetics on quiescent ring tension. Each pair of rings was then exposed to a single contractile agonist. Sequentially increasing cumulative doses of either serotonin (10^{-8} to 10^{-4} M), histamine (10^{-8} to 10^{-4} M), or prostaglandin $F_{2\alpha}$ (10^{-8} to 10^{-5} M) were added to the organ chambers. The isometric tension generated by the rings was measured.

The sequence in which the hearts were assigned to either halothane or isoflurane treatment was not randomized. It was initially believed that limited

Table 1. Characteristics of Patient Heart-Donors

	Patient										
Characteristic	A	B	C	D	E	F	G	H	I	J	K
Cardiac transplant	No	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes
Organ donor (NOT heart)	Yes	Yes	No	Yes	No	Yes	Yes	No	No	Yes	No
Diagnosis	Brain death	Brain death	Ischemic cardiomyopathy	Brain death	Idiopathic cardiomyopathy	Brain death	Brain death	Viral cardiomyopathy	Ischemic cardiomyopathy	Brain death	Ischemic cardiomyopathy
Age (yr)	41	51	42	32	24	34	32	34	51	25	53
Sex	M	F	M	M	F	M	F	F	M	F	M
LV ejection fraction (%)	—	25	18	—	20	—	30	23	22	50	20
Preoperative medications	None	None	Diltiazem Nitrates	None	Digoxin Furosemide Captopril	None	None	L-Dopa Captopril (both discontinued)	Diltiazem Nitrates Amiodarone	None	Digoxin Furosemide Nitrates Captopril
Intraoperative vasoactive drugs	Dopamine Vasopressin	Norepinephrine Dopamine	Norepinephrine Dobutamine Dopamine	None	None	Dopamine Vasopressin Phenylephrine	Dopamine Dobutamine	Dobutamine	None	Dopamine Vasopressin Phenylephrine	None
Anesthetics	Pancuronium	Pancuronium	Fentanyl Diazepam Pancuronium	None	Fentanyl Diazepam Pancuronium	Pancuronium	Pancuronium	Fentanyl Pancuronium	Sufentanil Vecuronium	Pancuronium	Fentanyl Midazolam Pancuronium Vecuronium
Coronary artery histology score[a]	2.1 ± 0.1	1.3 ± 0.1	1.8 ± 0.1	1.3 ± 0.3	0.6 ± 0.1	1.4 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.7 ± 0.1	0.8 ± 0.1	2.0 ± 0.1
Relaxation in response to 10^{-6} M bradykinin (%)	Not performed	2	0	30	12	21	0	2	6	17	0
Rings used in study of:	Halothane	Halothane	Halothane	Halothane	Isoflurane	Isoflurane	Isoflurane	Isoflurane	Halothane + isoflurane	Halothane + isoflurane	Halothane + isoflurane

LV, left ventricular.

[a] Scale of 0 (normal) to 3 (severely diseased) based on appearance on light microscopy examination. Data are expressed as mean ± SE, $n = 6$.

availability would restrict the study to investigation of halothane alone. Vessels from the first four hearts were used in halothane experiments. Subsequently, availability of hearts increased and vessels from the next four hearts were used in isoflurane experiments. The final three hearts provided rings for both isoflurane and halothane experiments.

At the end of the organ chamber studies, all coronary rings were transferred into a 10% formaldehyde solution, sliced, and stained with hematoxylin, phloxine, and safran for histologic examination. Rings were assessed by the same pathologist who determined a coronary artery histology score using the following criteria: (a) degree of luminal occlusion; (b) degree of fragmentation of the internal elastic lamina; (c) degree and distribution of vessel wall calcification; and (d) degree of intimal proliferation. Each feature was scored on a scale of 0 (normal) to 3 (severely diseased). The net coronary artery histology score for each ring was calculated using the four criteria of vessel damage.

Drugs

Serotonin (creatinine sulfate complex), histamine dihydrochloride, prostaglandin $F_{2\alpha}$, and bradykinin were obtained from Sigma Chemical Company (St. Louis, Mo.); they were prepared daily and diluted in distilled water. Halothane was obtained from Ayerst (New York, N.Y.) and isoflurane from Anaquest (Madison, Wis.).

Statistical Analysis

In all experiments, *n* equals the number of hearts from which rings were removed. Data are expressed as mean ± SEM. Statistical evaluation was performed by comparing integrated areas under the dose-response curves using analysis of variance. Paired *t*-tests were used to compare maximal contractile responses.

Table 2. Coronary Artery Histology Score[a]

Rings used for	Serotonin group	Histamine group	$PGF_{2\alpha}$ group
Isoflurane experiments	1.1 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
Halothane experiments	1.5 ± 0.1	1.2 ± 0.1	1.3 ± 0.1

Values are expressed as mean ± SEM, $n = 7$ hearts.
[a] Scale of 0 (normal) to 3 (severely diseased).

Table 3. Optimal Passive Tension in Grams Before Exposure to Anesthetics or to Contractile Agonists

Rings used for	Serotonin group	Histamine group	$PGF_{2\alpha}$ group
Isoflurane experiments	13.2 ± 0.5	13.1 ± 0.5	13.2 ± 0.5
Halothane experiments	11.0 ± 0.4	12.0 ± 1.3	10.7 ± 0.6

Values are expressed as mean ± SEM, $n = 7$ hearts.

Table 4. Tension Generated in Response to 40 mM KCl in Grams Before Exposure to Anesthetics or to Contractile Agonists (Control Contraction)

Rings used for	Serotonin group	Histamine group	$PGF_{2\alpha}$ group
Isoflurane experiments	13.6 ± 1.4	14.2 ± 1.5	13.8 ± 1.4
Halothane experiments	9.4 ± 1.2[a]	8.8 ± 1.5[a]	8.8 ± 1.7[a]

Values are expressed as mean ± SEM, $n = 7$ hearts.
[a] $P < 0.05$ compared with isoflurane experiments.

Table 5. Percent Relaxation of Rings Precontracted With 20 mM KCl to 10^{-6} M Bradykinin Before Exposure to Anesthetics or to Contractile Agonists

Rings used for	Serotonin group	Histamine group	$PGF_{2\alpha}$ group
Isoflurane experiments	12 ± 0	3 ± 1	9 ± 1
Halothane experiments	11 ± 1	7 ± 1	10 ± 1

Values are expressed as mean ± SEM, $n = 7$ hearts.

Results

A brief description of the patients from whom hearts were removed is provided in Table 1. Histologic appearance of the coronary artery segments and the responses to bradykinin are included. Characteristics of the coronary rings used in each phase of the experiment are shown in Tables 2–5, where histologic appearance, optimal passive tension, response to 40 mM KCl, and relaxation evoked by bradykinin are indicated. Except for the contractile responses to 40 mM KCl, differences between groups in terms of coronary artery histology score, optimal passive tension, and responses to bradykinin were small. How-

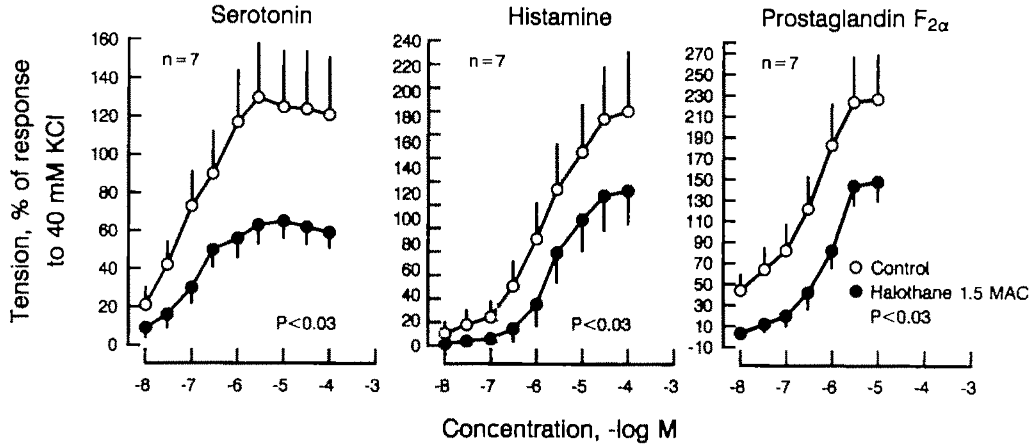


Figure 1. Concentration-response relationships of human coronary artery rings exposed to cumulative, increasing concentrations of serotonin, histamine, and prostaglandin $F_{2\alpha}$. Percentage contractions in the presence and absence of 1.5 MAC halothane are shown. Contractions are expressed as a percentage of a response to 40 mM KCl. Analysis of variance demonstrated statistically significant differences in responses of rings treated with halothane versus untreated rings ($P < 0.03$). Data are expressed as mean ± SEM. Seven hearts provided vessels for the experiments.

ever, in response to 40 mM KCl, rings used in the isoflurane experiments contracted more vigorously than those used to study halothane (Table 4).

Halothane 1.5 MAC

Halothane had no effect on the tension of quiescent rings. Addition of serotonin, histamine, or prostaglandin $F_{2\alpha}$ resulted in concentration-dependent contractions. Contractile responses to all three agonists were depressed by halothane (Figure 1).

Contractions were expressed as a percentage of the reference contraction obtained on stimulation with 40 mM KCl before exposure to anesthetics or to contractile agonists. Serotonin ($10^{-5.3}$ M) evoked 130% ± 28% contractions in untreated rings; in rings treated with halothane, the response was 63% ± 10% ($P < 0.03$). Histamine (10^{-4} M) evoked 183% ± 46% maximal contractions in untreated rings versus 121% ± 26% ($P < 0.05$) in rings treated with halothane. Prostaglandin $F_{2\alpha}$ (10^{-5} M) evoked 227% ± 42% contractions in untreated rings and 148% ± 18% ($P < 0.05$) in rings exposed to halothane. Comparison of integrated areas under the dose-response curves demonstrated that halothane treatment resulted in significant depression of contractions ($P < 0.03$).

Isoflurane 1.5 MAC

Isoflurane had no effect on the quiescent tension of unstimulated rings. Serotonin, histamine, and prostaglandin $F_{2\alpha}$ evoked concentration-dependent contractions. Isoflurane had no effect on the contractile responses (Figure 2). The maximum response to serotonin was 110% ± 16% of a reference contraction in untreated rings and 98% ± 16% in rings treated with isoflurane. For histamine, the responses were 106% ± 16% untreated and 123% ± 44% in treated rings; for prostaglandin $F_{2\alpha}$ the responses were 144% ± 13% untreated and 137% ± 11% in treated rings.

Coronary Artery Histology

Microscopy demonstrated histologic changes in vessels from all the hearts, including those from young, previously healthy donors. No heart studied provided completely normal coronary artery segments (Tables 1 and 2).

Discussion

The purpose of the investigation was to determine if 1.5 MAC halothane and 1.5 MAC isoflurane each attenuated contractions of isolated human coronary arteries evoked by serotonin, histamine, and prostaglandin $F_{2\alpha}$—three putative mediators of coronary constriction. It is important to note that experiments were performed using proximal, large epicardial conductance vessels—vessels that are involved in atherosclerosis. Experiments were not performed using small resistance arteries or arterioles. For this reason the experiments were not designed to test the effects

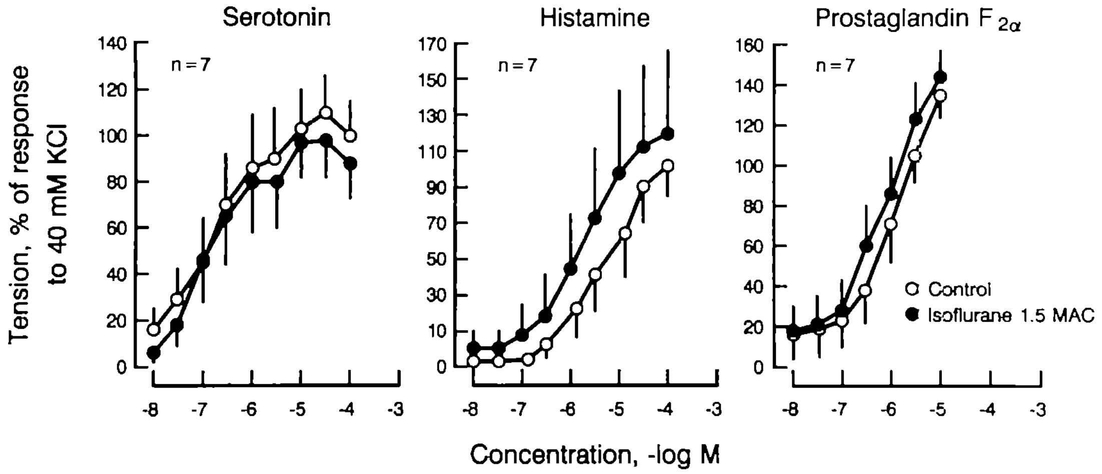


Figure 2. Concentration-response relationships of human coronary artery rings exposed to cumulative, increasing concentrations of serotonin, histamine, and prostaglandin $F_{2\alpha}$. Percentage contractions in the presence and absence of 1.5 MAC isoflurane are shown. Contractions are expressed as a percentage of a response to 40 mM KCl. Analysis of variance did not demonstrate differences in responses of rings treated with isoflurane versus untreated rings. Data are mean ± SEM. Seven hearts provided vessels for the experiments.

of isoflurane and halothane on mechanisms of "coronary steal" phenomena. Instead, they were designed to address the problem of active vasoconstriction of proximal epicardial coronary arteries—a condition that is thought to occur in patients with typical angina pectoris and during myocardial infarction (22). The findings indicate that 1.5 MAC halothane attenuated agonist-induced coronary artery contractions. Isoflurane 1.5 MAC had no effect on the contractile responses. The results of this experiment represent the first evidence that contractions of human coronary arteries are inhibited by halothane.

The use of human coronary arteries in the current experiment rather than those obtained from animals has advantages in that the study may more accurately reflect events occurring in patients with cardiac disease. However, experiments using human vessels can only be pursued at the expense of a number of inevitable difficulties. The most immediate problem is the limited availability of human hearts. Although the current experiments tested two anesthetics and employed three contractile agonists throughout a range of doses, limited availability of hearts restricted the study to only one anesthetic concentration—1.5 MAC. No dose-response relationships were established for the anesthetics.

A second problem concerned variability in the rings' responses to KCl. Before introducing the anesthetics, contractile characteristics of the rings were standardized using KCl, and these contractions were then used as a reference for expressing agonist-induced responses. This approach is an established method for quantitating contractile responses. In the current study, the rings used in the isoflurane studies responded more vigorously to KCl than did those used in the halothane experiments (Table 4). However, agonist-induced contractions in untreated rings did not differ significantly between isoflurane and halothane groups. Why the responses to KCl were variable is not known, although responses in human coronary arteries are often less homogeneous than those observed in vessels removed from animals (23). When tissue of animal origin is used, the animals providing the vessels are typically of the same weight, age, and breed, and have been exposed to the same environment, have eaten virtually identical diets, and have been treated with few, well-defined drugs. In contrast, the patients providing vessels for the current investigation were of different ages, from varied backgrounds, and with different lifestyles; they suffered from different illnesses and were treated with a variety of drugs. In addition, one subject was suspected of illegal drug use. In the current study, comparisons between halothane and isoflurane effects were not made because rings used in testing the two anesthetics differed in their baseline responses to KCl.

Isolated, histologically normal human coronary arteries relax in response to bradykinin (17). In the current experiment, absence of relaxation response to bradykinin in vessels removed from patients with ischemic cardiomyopathy was expected as atherosclerosis is known to impair endothelial function and inhibit endothelium-dependent relaxations (24). However, in the current investigation it was surprising that vessels removed from otherwise healthy but deceased patients, including 24- and 25-yr-old patients, also exhibited marked endothelial dysfunction. (Many of these segments, although free of atheroma, nevertheless exhibited a degree of histologic change when examined using light microscopy.) Early, subtle atherosclerotic changes are known to alter endothelium-dependent dilator responses in human beings (25). In addition, even the presence of risk factors for coronary artery disease can impair endothelium-dependent relaxations (26). However, in the current experiments, it is possible that the observed endothelial dysfunction resulted in part from cardiovascular instability before and after brain death. Acute brain trauma and brain death may result in episodes of both high and low arterial pressure. Acute hypertension has been shown to cause marked endothelial dysfunction in intact dogs, and morphologic and functional endothelial damage may occur after even transient episodes of hypertension (27).

It is unlikely that delays in harvesting the vessels caused endothelial dysfunction in the current experiment. Although smooth muscle contractile responses are preserved for at least 6 h in human coronary arteries obtained at autopsy, the endothelium of the human coronary artery is very labile and may soon after death lose the capacity to produce or release endothelium-derived relaxing factors (23). In the current experiments the hearts were removed in the operating room, were immediately placed in cold oxygenated Krebs-Ringer solution, and were then immediately transferred to the laboratory. The vessels were rapidly dissected free and were then also immediately placed in oxygenated electrolyte solution. The investigators have previously used this method with dog and pig coronary arteries and have observed preservation of endothelium-dependent responses.

The current investigation demonstrates that 1.5 MAC halothane attenuated contractions of human coronary arteries evoked by serotonin, histamine, and prostaglandin $F_{2\alpha}$ but does not provide information concerning the mechanism of this effect. The three agonists act on cell surface membrane receptors to stimulate phosphoinositide hydrolysis, second messenger generation, Ca^{2+} mobilization, calmodulin-dependent myosin light chain kinase activation, and, ultimately, actin and myosin crossbridge cycling (28,29). The site(s) at which halothane may act is not clearly established—although halothane has been shown to reduce Ca^{2+} availability in vascular smooth muscle by depleting the sarcoplasmic reticulum of Ca^{2+} (30). The results of the current experiment indicate that halothane has an effect on contractions evoked by specific agonists despite the absence of functioning endothelium.

Isoflurane 1.5 MAC had no effect on agonist-induced contractions of coronary arteries removed from human hearts. In isolated canine coronary arteries, isoflurane has been shown to attenuate contractions in an endothelium-dependent manner (18). Dysfunctional endothelium in the preparations used in the current experiment may account for the absence of isoflurane effect. Current results contrast with observations made in vivo in pigs, where isoflurane has been observed to attenuate contractions evoked by serotonin in vessels both with and without endothelium (10). However, the results are in agreement with findings obtained from isolated pig coronary arteries, where isoflurane has been found to exhibit less marked relaxant effects than halothane (9,10).

The results of the current investigation represent the first evidence that 1.5 MAC halothane attenuates agonist-induced contractions in coronary arteries isolated from the hearts of human beings. They also represent the first evidence that this effect occurs in vessels obtained from human beings. The results are suggestive of a potentially clinically advantageous effect of halothane. However, this preliminary evidence does not support the use of halothane as a replacement for established coronary artery vasodilator therapies.

References

1. Brown G, Bolson EL, Dodge HT. Dynamic mechanisms in human coronary stenosis. Circulation 1984;70:917–22.
2. Bolli R. Potential role of serotonin in dynamic coronary stenosis. J Am Coll Cardiol 1989;14:460–1.
3. Nabel EG, Ganz P, Gordon JB, Alexander RW, Selwyn AP. Dilation of normal and constriction of atherosclerotic coronary arteries caused by the cold pressor test. Circulation 1988;77:43–52.
4. Maseri A. Role of coronary artery spasm in symptomatic and silent myocardial ischemia. J Am Coll Cardiol 1987;9:249–62.
5. Gage JE, Hess OM, Murakami T, Ritter M, Grimm J, Krayenbuehl HP. Vasoconstriction of stenotic coronary arteries during dynamic exercise in patients with classic angina pectoris: reversibility by nitroglycerin. Circulation 1986;73:865–76.
6. Schwartz JS, Bache RJ. Pharmacologic vasodilators in the coronary circulation. Circulation 1987;75(Suppl I):I-162–7.
7. Willerson JT, Golino P, Eidt J, Campbell WB, Buja LM. Specific platelet mediators and unstable coronary artery lesions. Circulation 1989;80:198–205.
8. Blaise G, Sill JC, Nugent M, Van Dyke RA, Vanhoutte PM. Isoflurane causes endothelium-dependent inhibition of contractile responses of canine coronary arteries. Anesthesiology 1987;67:513–7.
9. Bollen BA, Tinker JH, Hermsmeyer K. Halothane relaxes previously constricted isolated porcine coronary artery segments more than isoflurane. Anesthesiology 1987;66:748–52.

10. Witzeling TM, Sill JC, Hughes JM, Blaise GA, Nugent M, Rorie DK. Isoflurane and halothane attenuate coronary artery constriction evoked by serotonin in isolated porcine vessels and in intact pigs. Anesthesiology 1990;73:100–8.
11. Vanhoutte PM, Shimokawa H. Endothelium-derived relaxing factor and coronary vasospasm. Circulation 1989;80:1–9.
12. Forman MB, Oates JA, Robertson D, Robertson RM, Roberts LJ II, Virmani R. Increased adventitial mast cells in a patient with coronary spasm. N Engl J Med 1985;313:1138–41.
13. Kalsner S, Richards R. Coronary arteries of cardiac patients are hyperreactive and contain stores of amines: a mechanism for coronary spasm. Science 1984;223:1435–7.
14. Rubanyi GM, Frye RL, Holmes DR, Vanhoutte PM. Vasoconstrictor activity of coronary sinus plasma from patients with coronary artery disease. J Am Coll Cardiol 1987;9:1243–9.
15. Van den Berg EK, Schmitz JM, Benedict CR, Malloy CR, Willerson JT, Dehmer GJ. Transcardiac serotonin concentration is increased is selected patients with limiting angina and complex coronary lesion morphology. Circulation 1989;79:116–24.
16. Pomerance A. Peri-arterial mast cells in coronary atheroma and thrombosis. J Pathol Bacteriol 1958;76:55–70.
17. Toda N, Okamura T. Endothelium-dependent and -independent responses to vasoactive substances of isolated human coronary arteries. Am J Physiol 1989;257:H988–95.
18. Toda N. Mechanism of histamine actions in human coronary arteries. Circ Res 1987;61:280–6.
19. Förstermann U, Mügge A, Bode SM, Frölich JC. Response of human coronary arteries to aggregating platelets: importance of endothelium-derived relaxing factor and prostanoids. Circ Res 1988;63:306–12.
20. Cherry PD, Furchgott RF, Zawadzki JV, Jothianandan D. Role of endothelial cells in relaxation of isolated arteries by bradykinin. Proc Natl Acad Sci USA 1982;79:2106–10.
21. Quasha AL, Eger EI, Tinker JH. Determination and application of MAC. Anesthesiology 1980;53:315–34.
22. Maseri A, Davies G, Hackett D, Kaski JC. Coronary artery spasm and vasoconstriction. The case for a distinction. Circulation 1990;81:1983–91.
23. Lüscher TF, Vanhoutte PM. Endothelium-dependent responses in human blood vessels. Tr Pharmacol Sci 1988;9:181–4.
24. Förstermann U, Mügge A, Alheid U, Haverich A, Frölich JC. Selective attenuation of endothelium-mediated vasodilation in atherosclerotic human coronary arteries. Circ Res 1988;62:185–90.
25. Werns SW, Walton JA, Hsia HH, Nabel EG, Sanz ML, Pitt B. Evidence of endothelial dysfunction in angiographically normal coronary arteries of patients with coronary artery disease. Circulation 1989;79:287–91.
26. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990;81:491–7.
27. Lamping KG, Dole WP. Acute hypertension selectively potentiates constrictor response of large coronary arteries to serotonin by altering endothelial function in vivo. Circ Res 1987;61:904–13.
28. Berridge MJ. Inositol triphosphate and diacylglycerol: two interacting second messengers. Ann Rev Biochem 1987;56:159–93.
29. Kamm KE, Stull JT. Regulation of smooth muscle contractile elements by second messengers. Ann Rev Physiol 1989;51:229–313.
30. Su JY, Zhang CC. Intracellular mechanisms of halothane's effect on isolated aortic strips of the rabbit. Anesthesiology 1989;71:409–17.

Chronic Verapamil Treatment Depresses Automaticity and Contractility in Isolated Cardiac Tissues

Zeljko J. Bosnjak, PhD, Jure Marijic, MD, David L. Roerig, PhD, David F. Stowe, MD, PhD, V. Shrinivas Murthy, MD, PhD, and John P. Kampine, MD, PhD

BOSNJAK ZJ, MARIJIC J, ROERIG DL, STOWE DF, MURTHY VS, KAMPINE JP. Chronic verapamil treatment depresses automaticity and contractility in isolated cardiac tissues. Anesth Analg 1991;72:462–8.

Chronically administered verapamil can accumulate in cardiac tissues and may depress cardiac function despite low plasma concentration. To examine this, two groups of rabbits were injected intraperitoneally twice a day with either 1 mg/kg verapamil or saline for 28 days. Fourteen hours after the last dose, right atrial tissue and right ventricular papillary muscle were isolated. Plasma and myocardial tissue concentrations of verapamil were determined. Plasma samples contained no detectable amounts of verapamil, but the myocardium contained 2.1 ± 0.6 (mean ± SE) ng of verapamil per gram of wet tissue. Spontaneous action potentials recorded from the sinoatrial node in the verapamil-treated group showed decreases in the phase 0 and phase 4 depolarization rates, a slower pacemaker rate, and an attenuated response to epinephrine compared with the saline-treated group. Papillary muscle in the verapamil-treated group exhibited a significantly lower force of contraction and a depressed contractile response to epinephrine compared with the control group. There were no differences in rate or contractile responses the day after single injection with 2 mg/kg verapamil or saline twice a day. Myocardial verapamil concentration increased with the duration of treatment and with the doses given; myocardial verapamil concentration was 3.0 ± 0.6 ng/g wet tissue in the group treated for 28 days with 2 mg/kg verapamil. Our study shows that chronic treatment of rabbits with verapamil decreases cardiac chronotropic and inotropic responses to adrenergic stimuli despite no detectable verapamil in plasma, and that accumulation of verapamil in the myocardium is probably associated with these effects.

Key Words: PHARMACOLOGY, VERAPAMIL. HEART, VERAPAMIL EFFECTS.

Acute administration of verapamil in vitro slows spontaneous sinoatrial (SA) nodal rate (1,2), decreases papillary muscle contractile performance (3), and depresses left ventricular pressure development in isolated hearts (4). Although knowledge of direct cardiac effects of verapamil after acute treatment is important, responses after chronic treatment may be substantially different. Hemodynamic effects and plasma levels after a single intravenous dose of verapamil suggest that this drug has a relatively short half-life of 2–5 h (5–7). Some unexpected observations have been reported during chronic oral treatment with verapamil. These are (a) a time delay between peak serum concentrations and peak cardiac effects (8); (b) a long duration of action after intravenous administration in cardiac patients (6); (c) a tissue accumulation of verapamil that is up to six times that in plasma (5); and (d) a half-life that is longer after chronic than after acute treatment (7), which may be only partially due to a decrease in hepatic clearance.

The in vitro effects of chronic administration of calcium channel blockers on automaticity of the SA node and on cardiac contractile function have not been reported. Our aims were to determine if chronic treatment of rabbits with verapamil results in accumulation of verapamil in cardiac tissue and to assess if tissue accumulation of verapamil is associated with attenuated chronotropic and inotropic responses to adrenergic receptor stimulation.

Methods

Studies were conducted on 44 New Zealand white rabbits of either sex weighing 3.7 ± 0.2 kg. Animals

---

Supported in part by the International Research Society (Z.J.B.), the National Institutes of Health grants HL01901 and HL34708 (Z.J.B.), and the VA Medical Center.

Received from the Anesthesiology Research Laboratory and the Departments of Anesthesiology and Physiology, The Medical College of Wisconsin and Veterans Administration Medical Center, Milwaukee, Wisconsin. Accepted for publication November 23, 1990.

Address correspondence to Dr. Bosnjak, Department of Anesthesiology, The Medical College of Wisconsin, MFRC, A1000, Milwaukee, WI 53226.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

were injected intraperitoneally either with 1 or 2 mg/kg (2 mg/mL) verapamil or with 0.5 mL saline twice a day for 1, 7, 14, or 28 days. Physiologic studies were performed only on those animals treated with 2 mg/kg verapamil for 1 day and with 1 mg/kg for 28 days. We conducted primarily in vitro physiologic studies because in in vivo animal preparations heart rate and contractile responses to verapamil can be altered as a result of reflex baroreceptor-mediated adrenergic stimulation (9) and because direct effects in isolated tissues could be easily compared.

Fourteen hours after the last injection of verapamil, rabbits were anesthetized with sodium pentobarbital (35–40 mg/kg); the hearts were quickly removed, and the aorta was perfused with cold oxygenated Krebs' solution. After isolation, the tissues were mounted in tissue baths and suffused continuously at a rate of 10 mL/min with modified Krebs' solution containing (in mM): Na^+ 137; K^+ 3.0; Ca^{2+} 2.5; Mg^{2+} 1.2; Cl^- 134; HCO_3^- 15.5; HPO_4^{2-} 1.2; EDTA 0.05; and glucose 11.5. The solution was equilibrated in a reservoir with 97% O_2–3% CO_2 and was maintained at 37°C and pH 7.4 ± 0.05. Suffusate oxygen tension was maintained at greater than 500 mm Hg.

As described in previous studies (3), right ventricles from control and from verapamil-treated rabbits were opened and uniformly thin (<1 mm diameter) papillary muscle strips were selected. The muscles were mounted horizontally in the suffusion chamber by pinning one end and fixing the other end to a force transducer. The muscles were stimulated by placing bipolar stimulating electrodes at one end of the muscle and connecting them to a stimulus isolation unit. Resting length of both muscle strips was adjusted to obtain maximal developed contractile force during a test twitch. Square-wave 2-ms pulse stimuli were applied at two times the threshold current and were maintained for 3-min periods at 2-, 1-, 0.8-, and 0.6-s pacing intervals, which correspond to pacing rates of 30, 60, 75, and 100 beats/min. During the 15–20-min equilibration periods (controls), muscles were paced at 15 beats/min. Along with isometric contractile force measurements, the following transmembrane action potential characteristics of control and verapamil-treated papillary muscles were measured with glass microelectrodes (1) during pacing at 15 beats/min: resting membrane potential, slope of depolarization of phase 0, and action potential duration measured at 50% repolarization. Inotropic responses of papillary muscle from control and treated rabbits to exogenous epinephrine, 0.05–0.2 μg/mL, were examined after baseline values were obtained. Epinephrine was used to simulate an increase in β-adrenergic drive by the autonomic nervous system in vivo.

From the same hearts the right atrium containing the SA node was isolated and suffused as described in previous studies (1,2). Transmembrane action potentials from verapamil-treated and from control SA nodal tissues were measured simultaneously under identical suffusate conditions using two intracellular recording electrodes. Membrane potentials were measured with glass microelectrodes filled with 3M KCl having tip resistances of 40–80 MΩ (1). Variables measured were rate of spontaneous SA nodal discharge, slope of slow diastolic depolarization (phase 4), slope of rapid depolarization (phase 0), and maximal diastolic potential. Chronotropic responses of SA nodal tissue from verapamil-treated and control rabbits to exogenous 0.1–25 μg/mL epinephrine were also examined after baseline values were obtained.

In addition to the above in vitro studies after chronic (28 days) verapamil treatment, in vivo and in vitro studies were performed during acute treatment and after a 1-day administration of verapamil. In the in vivo studies, heart rate and PR intervals were measured from the electrocardiogram in conscious animals before and immediately after intraperitoneal injection of 1 mg/kg verapamil. In the acute 1-day verapamil studies, six hearts were isolated 14 h after the second twice-a-day dose of 2 mg/kg, and contractile force development and action potential characteristics of isolated right papillary muscle at different pacing rates and during increasing epinephrine concentration were examined. The responses in each verapamil-treated muscle were compared with the responses in the control muscles placed in the same bath. Action potential characteristics in verapamil-treated and control SA nodal tissues from the same hearts were also examined during control and during increasing epinephrine concentrations.

In another group of 24 rabbits, plasma was collected and hearts were isolated 14 h after the last verapamil treatment of 1 or 2 mg/kg after twice daily treatment for 7, 14, or 28 days. Plasma and isolated hearts were perfused briefly with Krebs' solution to remove blood; plasma and hearts were quickly frozen and were later analyzed for verapamil concentration using a high-pressure liquid chromatographic method as described previously (10).

Effects of verapamil on muscle contractility and on SA pacemaker rate were analyzed by applying two-way analysis of variance techniques to determine significance between and within animal groups. Differences among means were analyzed by least signif-

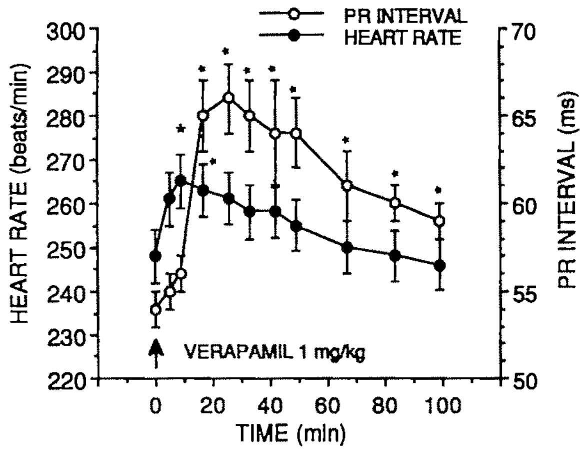


Figure 1. Mean heart rates and PR intervals in conscious rabbits given an intraperitoneal injection (*arrow*) of 1 mg/kg verapamil ($n = 5$). *$P < 0.05$ vs zero time.

Table 1. Myocardial Verapamil Concentration (ng/g Wet Heart Weight)

Days of treatment	1 mg/kg bid	2 mg/kg bid
7	0.61 ± 0.34	0.94 ± 0.49
14	0.79 ± 0.25	1.39 ± 0.17[a]
28	2.05 ± 0.56[b,c]	2.95 ± 0.56[b,c]

Values are mean ± SEM. $n = 4$ for each mean value.

Physiologic studies were conducted only in rabbits treated twice a day (bid) for 28 days with 1 mg/kg verapamil ($n = 7$) or the saline control ($n = 7$). Verapamil was not detectable in plasma 14 h after the last injection of either dose of verapamil with any duration of administration.

[a] $P < 0.05$ compared with 1-mg/kg bid group.

[b] $P < 0.05$ compared with 7-day treatment.

[c] $P < 0\ 05$ compared with 14-day treatment.

icant difference tests. Differences in myocardial tissue concentrations of verapamil between groups treated with 1 and 2 mg/kg verapamil twice a day for 7, 14, or 28 days were analyzed by Student's paired *t*-tests; differences in tissue concentration of verapamil among the three treatment periods at a given dose regimen were assessed by two-way analysis of variance. Slopes of contractile force or SA nodal rate as a function of epinephrine or pacing were determined by regression analyses of individual data points. Slopes were compared for parallelism by Student's *t*-tests. All data are expressed as mean ± SE. Statistical significance was designated at the $P < 0.05$ level for all data.

Results

Mean wet heart weights were not significantly different in saline-treated (5.9 ± 0.6 g) and in verapamil-treated (5.8 ± 0.4 g) groups after 28 days of treatment. There was no difference in muscle cross-sectional area (0.90 ± 0.04 vs 0.91 ± 0.05 mm^2) in the saline-treated ($n = 7$) and verapamil-treated ($n = 7$) groups.

Acute In Vivo and 1-Day In Vitro Responses to Verapamil

Intraperitoneal injection of a single 1-mg/kg dose of verapamil to conscious rabbits produced an immediate increase in heart rate lasting about 30 min (Figure 1). At the same time, the PR interval increased significantly and remained elevated up to 1 h later. Heart rate and PR interval were unchanged with intraperitoneal injection of saline (data not shown). There was no statistical difference in the maximal contractile force responses of papillary muscles examined 14 h after the second injection of 2 mg/kg verapamil or saline at each pacing rate (data not shown). For example, during the 100-beats/min pacing period, peak contractile force was 8.9 ± 0.8 and 9.2 ± 1.1 mN/mm^2 for the control and verapamil-treated groups, respectively. Baseline SA nodal action potential and rate responses, and responses to increasing doses of epinephrine, were also similar in the two groups (data not shown). For example, sufusion of solution containing 1 μg/mL epinephrine increased SA nodal pacing rate from 202 ± 4 to 260 ± 9 beats/min in the verapamil group and similarly from 203 ± 5 to 268 ± 8 beats/min in the control group.

Plasma and Cardiac Muscle Verapamil Concentrations

Myocardial tissue concentration of verapamil as a function of the concentration injected and the duration of administration between 7 and 28 days is presented in Table 1. The 2-mg/kg twice-a-day dose produced a higher myocardial level than the 1-mg/kg twice-a-day dose after 14 days, but this did not reach significance at 28 days. Verapamil was not detectable in plasma 14 h after the last injection of either dose of verapamil or with any duration of administration.

Heart Rate and Contractile Responses to Epinephrine and Pacing

The spontaneous rate of isolated SA nodal tissue from saline-treated rabbits (202 ± 4 beats/min) was significantly higher than it was in tissues from rabbits treated for 28 days with 1 mg/kg verapamil twice a day (183 ±

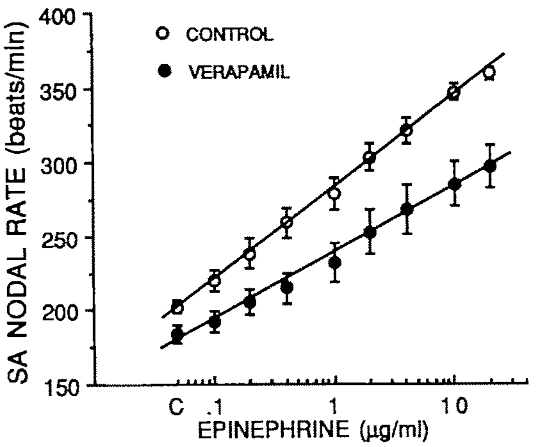


Figure 2. Effects of epinephrine on spontaneous SA nodal rates in nodal tissue from control and verapamil-treated rabbits (1 mg/kg twice a day for 28 days). Regression coefficients and slopes (beats·min^{-1}/µg·mL^{-1}), respectively, were 0.998 and 61.4 (control) and 0.996 and 45.3 (verapamil). Both slopes are significantly different from zero and significantly different from each other, $P < 0.05$); $n = 7$.

6 beats/min). Sinoatrial nodal rate responses in saline- and chronic verapamil-treated groups to increasing concentrations of epinephrine are shown in Figure 2. The maximal SA nodal rate with 11 µg/mL epinephrine was 359 ± 4 beats/min in the control group and 297 ± 14 beats/min in the verapamil group; the slope of the rate/log epinephrine dose-response was significantly less in the chronic verapamil group.

Baseline (epinephrine-free) papillary muscle contractile force during pacing at the baseline rate of 15 beats/min was not significantly different between verapamil-treated rabbits and saline-treated controls. Contractile force during suffusion with graded concentrations of epinephrine (0.05, 0.1, and 0.2 µg/mL) increased significantly in both groups, but this increase was significantly less in the verapamil-treated group (Figure 3). In addition, the slope of the force/epinephrine dose-response was significantly less in the chronic verapamil-treated group.

Contractile force responses of papillary muscles to increasing pacing rates are shown in Figure 4. Baseline rate was 15 beats/min. Increasing the rate of pacing produced increases in contractile force at each of three rates in the control group and in the two highest rates in the verapamil-treated group; the slope of the force/rate response was significantly less in the chronic verapamil-treated group.

Action Potential Responses in Papillary Muscle and Sinoatrial Nodal Fibers

Action potential characteristics obtained by transmembrane recordings of papillary and SA nodal cells are displayed in Table 2. Chronic verapamil treatment caused significant decreases in dV/dt$_{max}$ during phase 0 of the action potential upstroke of both SA nodal tissue and papillary muscle. The rate of the phase 4 diastolic depolarization of SA nodal cells was also attenuated and associated with a slowing of the pacemaker rate. Sinoatrial nodal diastolic membrane potential was unchanged, and resting papillary muscle membrane potential was slightly but significantly depolarized after chronic verapamil treatment.

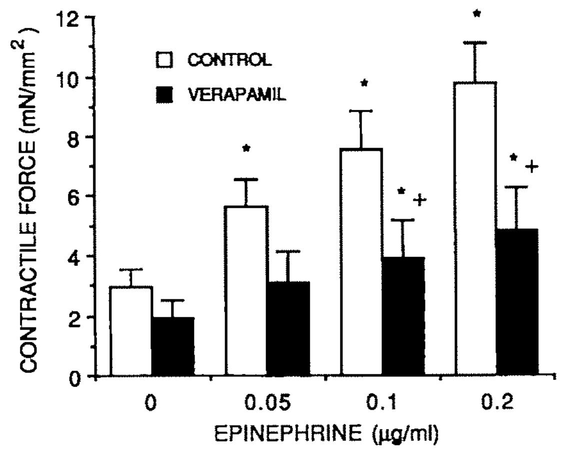


Figure 3. Isometric contractile force responses to epinephrine in isolated right ventricular papillary muscle from control and verapamil-treated rabbits (1 mg/kg twice a day for 28 days). Pacing rate was 15 beats/min. $^{*}P < 0.05$ vs epinephrine-free controls; $^{+}P < 0.05$ vs control for verapamil; $n = 7$.

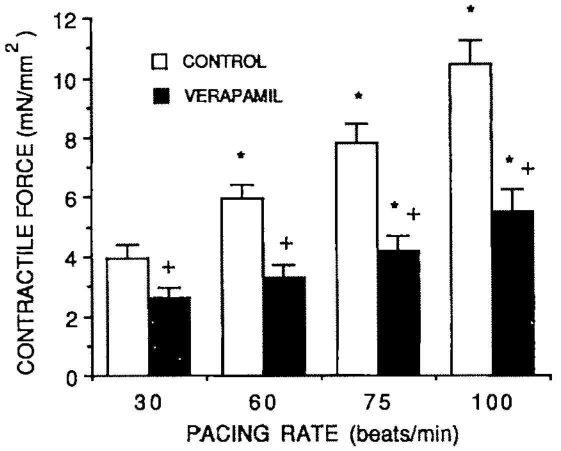


Figure 4. Isometric contractile force responses to different pacing rates in papillary muscle obtained from control and verapamil-treated rabbits. $^{*}P < 0.05$ vs 30 beats/min; $^{+}P < 0.05$ vs control; $n = 7$.

Discussion

We examined changes in myocardial contractility, SA nodal rate, and action potential characteristics of

Table 2. Effects of Verapamil on Myocardial Action Potentials

Group	Phase 4 (mV/s)	Phase 0 (V/s)	Em (mV)
SA node			
Control	147 ± 5	1.62 ± 0.06	−55.3 ± 1.2
Verapamil-treated	85 ± 4[a]	1.01 ± 0.03[a]	−54.0 ± 0.8
Group	APD_{50} (ms)	Phase 0 (V/s)	Em (mV)
Papillary muscle			
Control	64.3 ± 1.5	330 ± 6	−82.2 ± 0.4
Verapamil-treated	68.8 ± 2.0	275 ± 10[a]	−80.5 ± 0.4[a]

Values are mean ± SE.

Rabbits were pretreated with 1 mg/kg verapamil or saline (control) twice a day for 28 days. Tissues from control and treated rabbits were studied simultaneously in the same bath. Sinoatrial nodal rates were 202 ± 4 beats/min (control) and 183 ± 6 beats/min (verapamil). Muscles were paced at 30 beats/min (n = 7 hearts/group). Three impalements for each sinoatrial nodal tissue and seven impalements for each papillary muscle.

[a] $P < 0.05$ vs control groups.

cardiac tissues isolated from rabbits after acute and chronic treatment with verapamil. Chronic (28 day) verapamil treatment significantly attenuated both papillary muscle contractile force by about 50%, at pacing rates of 60 beats/min, and spontaneous SA nodal rate by about 8%. Moreover, chronic treatment with verapamil attenuated increases in SA nodal rate and in papillary muscle contractility due to increasing doses of epinephrine. These changes were accompanied by the presence of verapamil in myocardial tissue but not in plasma. These effects were a consequence of chronic rather than of acute verapamil treatment. This is supported by the lack of in vitro cardiac effects of 2 mg/kg verapamil twice a day after 1 day of treatment. The immediate increase in heart rate in conscious rabbits after injection of verapamil probably reflects a baroreflex response to lowered blood pressure with vasodilation (11). The increase in PR interval may be due to a direct effect of verapamil on the AV node, as well as to an indirect rate-dependent effect.

Increasingly, a large number of patients are being treated with calcium channel blockers for a variety of cardiovascular diseases (7,12). Cardiac effects of these agents include depression of SA and AV nodal automaticity, prolongation of AV conduction time, and suppression of the rate of ectopic impulse discharge (1,4,7,13,14). Although these agents act similarly to block the action potential-dependent calcium channel, their obvious chemical heterogeneity suggests that several sites and mechanisms of action exist (9). Acutely, the calcium channel blockers act basically to inhibit the slow transsarcolemmal Ca^{2+} influx while having only a slight effect on the fast Na^+ current that initiates the normal myocardial action potential upstroke (1,2). In addition to decreasing Ca^{2+} conductivity, verapamil and diltiazem alter the kinetics of reactivation of the slow channels. Nifedipine acts by reducing only the number of available slow channels for Ca^{2+} transport while remaining available channels function normally (15). For these reasons, the effects of verapamil and diltiazem, but not of nifedipine, are dependent on heart rate.

The increased use of calcium channel blockers is related to the recognized importance of calcium as a mediator of automaticity and contractile force and to the effectiveness of calcium channel blockers on reducing myocardial ischemia by reducing heart rate and contractile force and by causing vasodilatation. These effects reduce oxygen and nutrient demand and increase oxygen supply. Our finding that chronic verapamil treatment significantly depresses the increase in contractile force of papillary muscle with increasing rates of contraction (i.e., the positive staircase effect) contrasts with results in studies in which verapamil is directly added to the superfusion medium. With acute administration, verapamil reverses the positive staircase effect such that progressively lower isometric force development is generated at higher stimulation frequencies (16). It appears that as stimulation rate is increased in the presence of verapamil, the reduced rate of recovery of the calcium channel results in a progressive decrease in transsarcolemmal calcium flux with a subsequent decrease in contractile force (17). Indeed, verapamil not only reduces transmembrane calcium influx but also attenuates the rate of recovery of the calcium channel after a period of inactivation (18).

Besides their primary effects on the cell membrane, calcium channel blockers appear to have intracellular effects, the exact nature and importance of which are unclear (12,16). Although verapamil does not appear to alter calcium release from sarcoplasmic reticulum in myocardial preparations utilizing skinned muscle (19), there are data that suggest that verapamil acts by mechanisms other than inhibition of inward calcium flux (6). Verapamil may have sites of action in addition to a membrane site, i.e., intracellular effects, but there is no clear evidence for this at this time. We did not determine whether the verapamil concentration measured in cardiac tissue was bound extracellularly or located intracellularly. If verapamil accumulates on the extracellular surface, it might slow influx at the calcium channel. Our results with the faster pacing rates suggest that the slow inward current, but not its rate of recovery, is affected. For example, verapamil has been shown to slow the restitution kinetics of calcium availability from internal stores (20). Whether diltiazem and nifedipine also accumulate in cardiac tissues with chronic treatment and cause cardiac depression remains to be investigated.

An understanding of the heart rate and contractile effects of chronic treatment with calcium channel blockers is important because significant depression of chronotropic and inotropic effects may remain after the treatment is discontinued. During chronic administration of verapamil to patients, there is an increased plasma half-life along with myocardial accumulation of the drug (11). The therapeutic plasma concentration of verapamil is difficult to predict because the pharmacologic effects of verapamil accumulated in myocardial cells might contribute to the overall therapeutic response. Myocardial accumulation of verapamil might develop from at least two kinetically different tissue stores: (a) acute accumulation at rapidly reversible binding sites that are depleted rapidly with falling plasma levels; and (b) chronic accumulation at slowly reversible binding sites that are depleted only slowly even though the plasma contains no detectable amount of verapamil.

Potent volatile anesthetics decrease cardiac automaticity (1,2,4), conduction (4,21), and contractility (3,4,22–24). Acutely, volatile anesthetics alter verapamil pharmacokinetics (25) and have additive effects with verapamil on cardiac contractile function, automaticity, and conduction (3,4,25–27). After chronic exposure to verapamil, it is expected that myocardial depression produced by volatile anesthetics would be augmented.

Our study indicates an association between the tissue concentration of verapamil and a decrease in baseline cardiac function and in the responsiveness to epinephrine. Although this association does not necessarily imply a cause-and-effect relationship, our results do suggest the possibility that cardiac function in vivo can be depressed after chronic verapamil treatment and that the response to adrenergic nervous stimulation can be blunted. Changes in autonomic responsiveness, peripheral vascular tone, and other extrinsic cardiac influences during chronic verapamil treatment may underlie, at least in part, the effects we have observed in vitro.

References

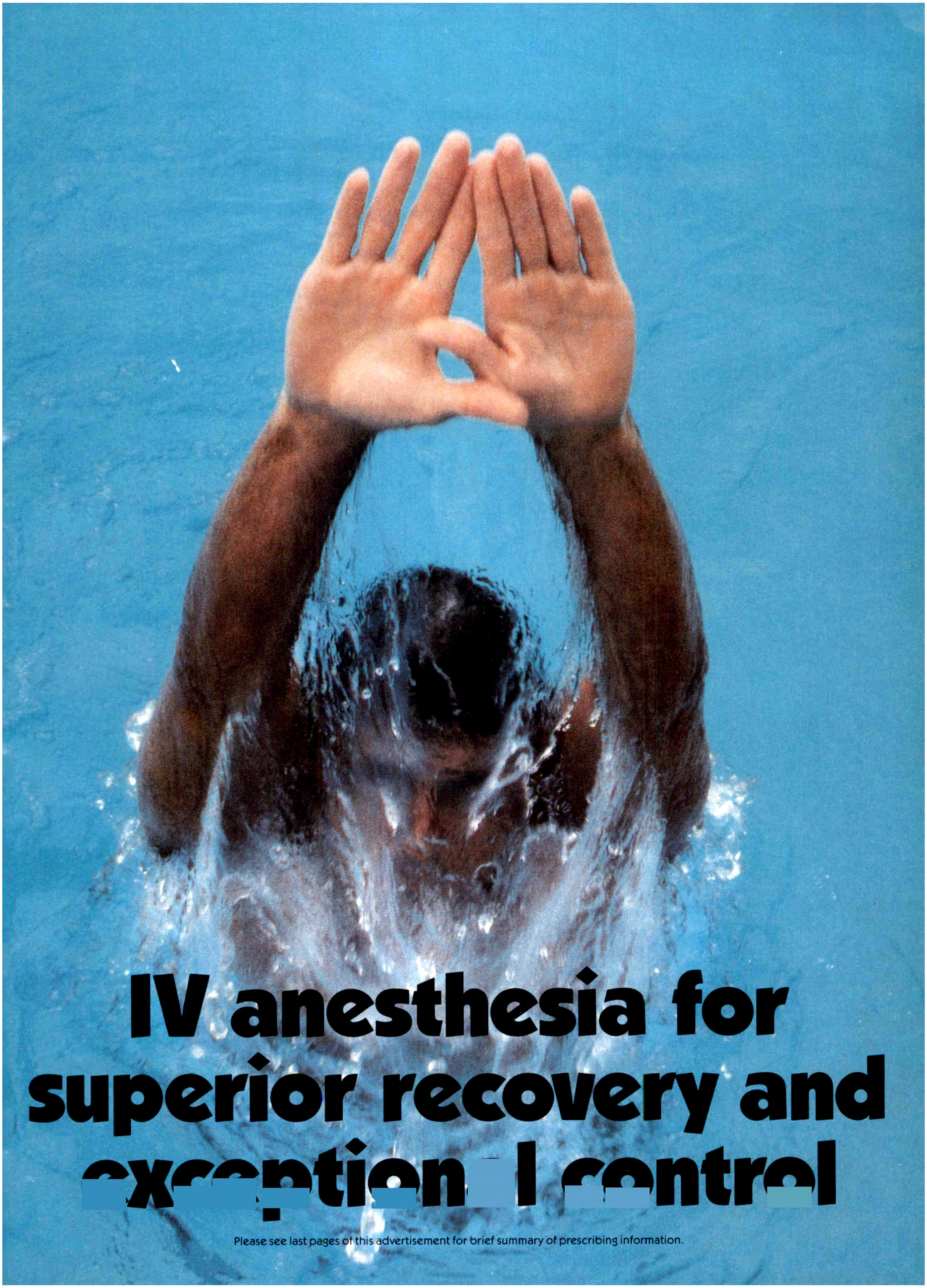
1. Bosnjak ZJ, Kampine JP. Effects of halothane, enflurane and isoflurane on the SA node. Anesthesiology 1983;158:314–21.
2. Stowe DF, Dujic Z, Bosnjak ZJ, Kalbfleisch JH, Kampine JP. Volatile anesthetics attenuate sympathomimetic actions on the guinea pig SA node. Anesthesiology 1988;68:887–94.
3. Bosnjak ZJ, Kampine JP. The effects of halothane on transmembrane potentials, Ca^{2+} transients and papillary muscle tension in the cat. Am J Physiol 1986;251:H374–81.
4. Marijic J, Bosnjak ZJ, Stowe DF, Kampine JP. Effects and interaction of verapamil and volatile anesthetics on the isolated perfused guinea pig heart. Anesthesiology 1988;169:914–22.
5. Kates RE, Keefe DLD, Schwartz J, Harapat S, Kirsten EB, Harrison DC. Verapamil disposition kinetics in chronic atrial fibrillation. Clin Pharmacol Ther 1981;30:44–51.
6. Schwartz JB. Verapamil in atrial fibrillation. The expected, the unexpected, and unknown. Am Heart J 1983;106:173–6.
7. Schwartz JB, Keefe DL, Kirsten E, Kates RE, Harrison DC. Prolongation of verapamil elimination kinetics during chronic oral administration. Am Heart J 1982;104:198–203.
8. Reiter MJ, Shand DG, Aanonsen LM, Wagoner R, McCarthy E, Pritchett ELC. Pharmacokinetics of verapamil. Experience with a sustained intravenous infusion regimen. Am J Cardiol 1982; 50:716–21.
9. Millard RW, Lathrop DA, Grup G, Ashraf M, Grup IL, Schwartz A. Differential cardiovascular effects of calcium channel agents: potential mechanisms. Am J Cardiol 1982;49:499–506.
10. Roerig DL, Kotrly KJ, Dawson CA, Ahlf SB, Gualtieri JF, Kampine JP. First-pass uptake of verapamil, diazepam, and thiopental in the human lung. Anesth Analg 1989; 69:461–6.
11. Murthy VS, Zagar ME, Vollmer RR, Schmidt DH. Pentobarbital-induced changes in vagal tone and reflex activity in rabbits. Eur J Pharmacol 1982;184:41–50.
12. Fleckenstein A. History of calcium antagonists. Cir Res 1983; 52(Suppl 2):3–16.
13. Rosen MR, Wit AL, Hoffman BF. Appraisal and reappraisal of cardiac therapy. Electrophysiology and pharmacology of cardiac arrhythmias. VI. Cardiac effects of verapamil. Am Heart J 1975;89:665–73.
14. Vasalle M. Cardiac automaticity and its control. In: Levy MN, Vassalle M, eds. Excitation and neural control of the heart. Chapter 3. Baltimore: Waverly Press, 1982:59–77.
15. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. Am J Cardiol 1980;146: 1047–55.
16. Church J, Zsoter TT. Calcium antagonistic drugs. Mechanism of action. Can J Physiol Pharmacol 1980;158:254–64.
17. Nayler WG, Mas-Oliva J, Williams AJ. Cardiovascular receptors and calcium. Circ Res 1980;46(suppl):161–6.
18. Kohlhardt M, Mnich Z. Studies of the inhibitory effect of verapamil on the slow inward current in mammalian ventricular myocardium. J Mol Cell Cardiol 1978;10:1037–52.
19. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Ann Rev Pharmacol Toxicol 1977;117:149–66.
20. Bayer R, Hennekes R, Kaufmann R, Mannhold R. Inotropic and electrophysiological actions of verapamil and D600 in mammalian myocardium. Naunyn Schmiedebergs Arch Pharmacol 1975;290:49–68.
21. Atlee JL, Bosnjak ZJ. Mechanisms for cardiac dysrhythmias during anesthesia. Anesthesiology 1990;72:347–74.
22. Lynch C III. Differential depression of myocardial contractility by halothane and isoflurane in vitro. Anesthesiology 1986;64: 620–31.
23. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: a review of possible mechanisms. Anesthesiology 1987;67:745–66.
24. Bosnjak ZJ, Aggarwal A, Turner LA, Kampine JP. Differential effects of halothane, enflurane and isoflurane on Ca^{2+} tran-

sients and papillary muscle tension in the guinea pig (abstract). Anesthesiology 1988;69:A88.

25. Chelly JE, Hysing ES, Abernethy DR, Doursout M-F, Merin RG. Effects of inhalational anesthetics on verapamil pharmacokinetics in dogs. Anesthesiology 1986;65:266–71.

26. Kapur PA, Bloor BC, Flacke WE, Olewine SK. Comparison of cardiovascular responses to verapamil during enflurane, isoflurane, or halothane anesthesia in the dog. Anesthesiology 1984;61:156–60.

27. Atlee JL, Hamann SR, Brownlee SW, Kreigh C. Conscious state comparisons of the effects of the inhalation anesthetics and diltiazem, nifedipine, or verapamil on specialized atrioventricular conduction times in spontaneously beating dog hearts. Anesthesiology 1988;68:519–28.



Please see last pages of this advertisement for brief summary of prescribing information.

Superior
exceptional

Significantly improved speed and quality of recovery compared with thiopental/isoflurane

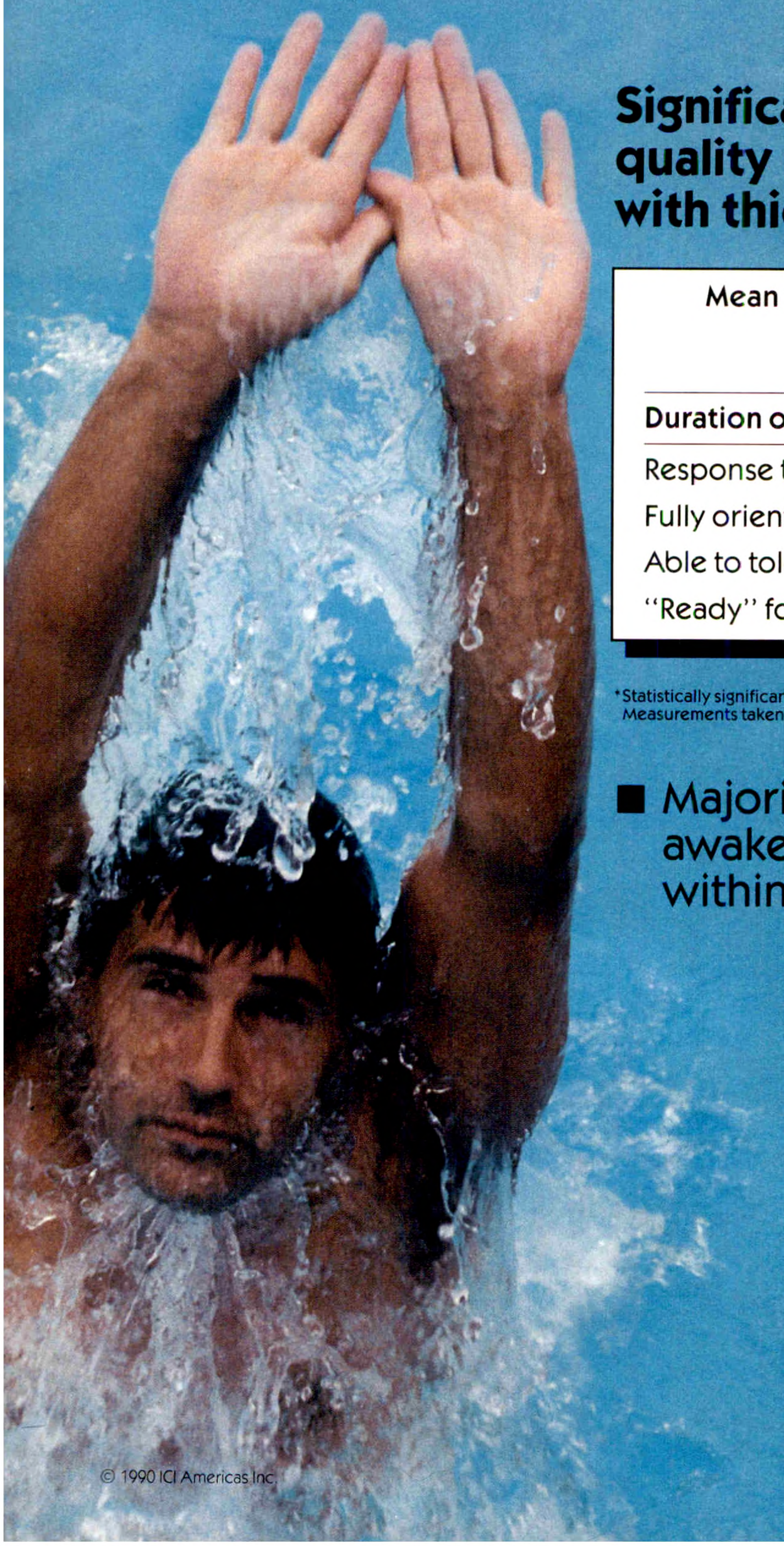
Mean postanesthesia recovery times (min)[1]

	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	**85***	**57**
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564[1]

*Statistically significant ($P < .05$).
Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes



© 1990 ICI Americas Inc.

recovery and anesthetic control

Significantly less nausea and vomiting than with thiopental/isoflurane

	DIPRIVAN	Thiopental/ isoflurane
Wetchler[2]	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al[3]	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®

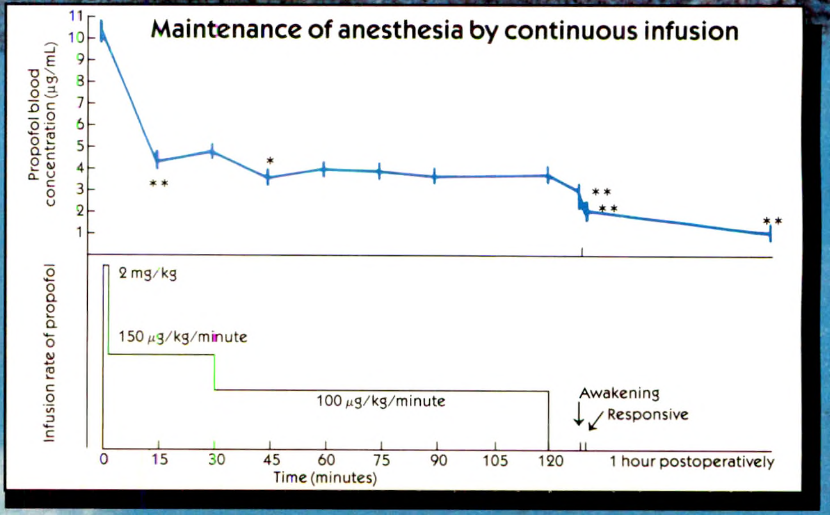
INJECTION

propofol

Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



Maintenance of anesthesia by continuous infusion

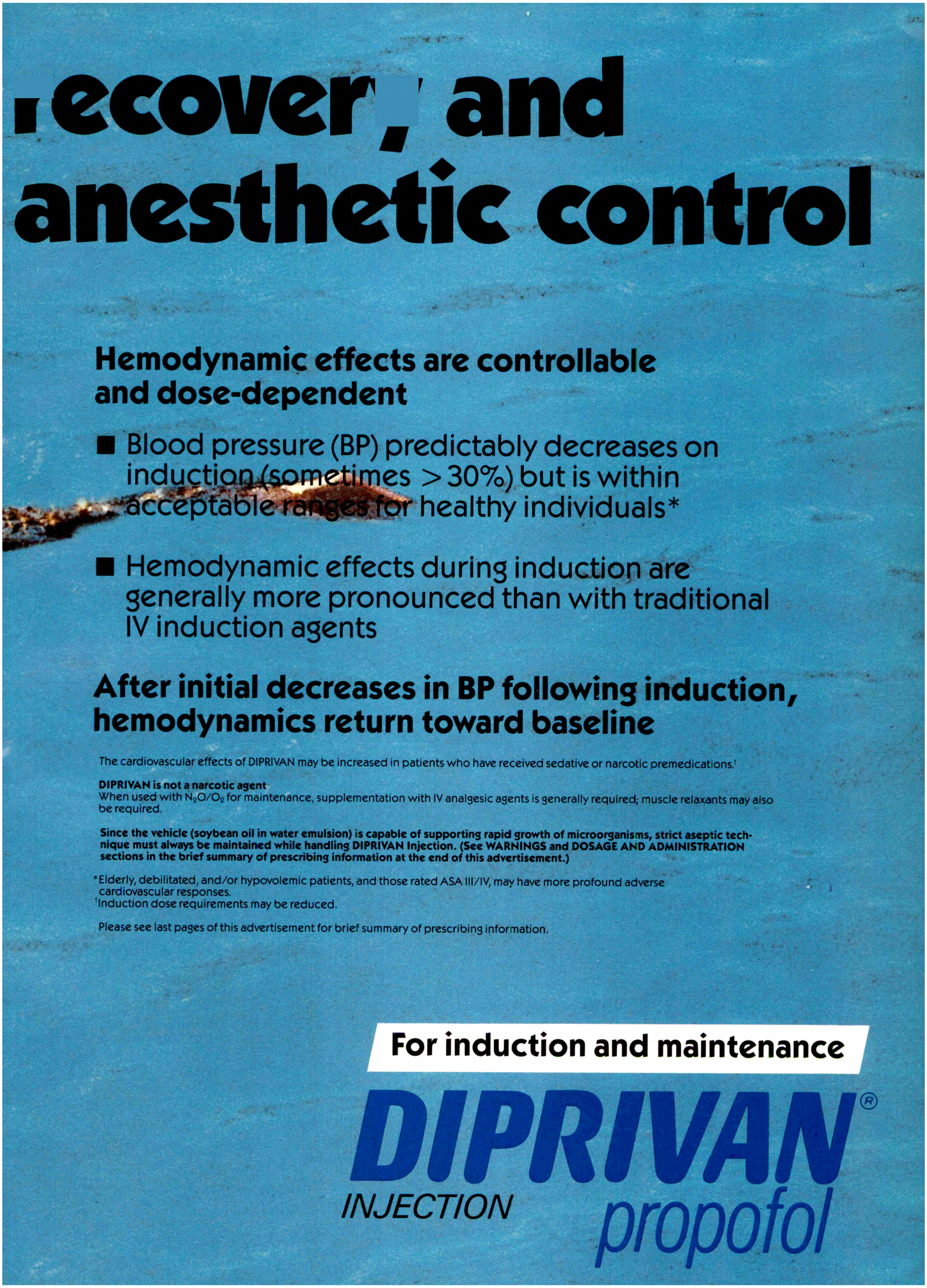
—adapted from Herregods et al, p 364[4]

*Significant difference ($P < .05$) from previous value.
**$P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 μg/kg/min for 30 minutes—then 100 μg/kg/min for 90 minutes.[4]

- Total body clearance exceeds estimates of hepatic blood flow[5]
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.



recovery, and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes >30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.[†]

DIPRIVAN is not a narcotic agent
When used with N_2O/O_2 for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Since the vehicle (soybean oil in water emulsion) is capable of supporting rapid growth of microorganisms, strict aseptic technique must always be maintained while handling DIPRIVAN Injection. (See WARNINGS and DOSAGE AND ADMINISTRATION sections in the brief summary of prescribing information at the end of this advertisement.)

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.
[†] Induction dose requirements may be reduced.

Please see last pages of this advertisement for brief summary of prescribing information.

For induction and maintenance

DIPRIVAN®
INJECTION
propofol

For induction and maintenance

DIPRIVAN®

INJECTION propofol

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique, **DIPRIVAN is a cost-effective alternative to thiopental/isoflurane for induction and maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

References: 1. Korttila K, Faure E, Apfelbaum J, Ekdawi M, Prunskis J, Roizen M. Recovery from propofol versus thiopental-isoflurane in patients undergoing outpatient anesthesia. *Anesthesiology.* 1988;69(3A):A564. Abstract. 2. Wetchler BV. A comparative evaluation of recovery following anesthesia with Diprivan® (propofol) by intravenous infusion versus Diprivan® followed by isoflurane versus thiopental sodium followed by isoflurane for short surgical procedures. Data on file, Stuart Pharmaceuticals, Wilmington, Delaware. 3. Sung YF, Reiss N, Tillette T. The differential cost of anesthesia and recovery with propofol-nitrous oxide anesthesia versus thiopental-isoflurane-nitrous oxide. *Anesth Analg.* 1990;70:S396. Abstract. 4. Herregods L, Rolly G, Versichelen L, Rosseel MT. Propofol combined with nitrous oxide-oxygen for induction and maintenance of anaesthesia. *Anaesthesia.* 1987;42:360-365. 5. Cockshott ID. Propofol ('Diprivan') pharmacokinetics and metabolism: an overview. *Postgrad Med J.* 1985;61(suppl 3):45-50.

Please see last pages of this advertisement for brief summary of prescribing information.

STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN®

INJECTION
10 mg/mL
propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery.

DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See PRECAUTIONS.)

DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See PRECAUTIONS.)

CONTRAINDICATIONS: When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components.

WARNINGS: DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.**

DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known.

Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See DOSAGE AND ADMINISTRATION, Handling Procedures.)

PRECAUTIONS: General: A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See DOSAGE AND ADMINISTRATION.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis.

Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home.

Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae.

Perioperative myoclonia, rarely including opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered.

Rarely, a clinical syndrome which may include bronchospasm and erythema accompanied by hypotension has occurred shortly after the administration of DIPRIVAN Injection, although the use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear.

Drug Interactions: As DIPRIVAN Injection has no vagolytic activity, premedication has usually included anticholinergic agents (eg, atropine or glycopyrrolate) to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli.

The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output.

During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection.

DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants).

No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal carcinogenicity studies have not been performed with propofol.

In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae,* in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test.

Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus.

Nursing Mothers: DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known.

Pediatric Use: DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established.

Neurosurgical Anesthesia: Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures.

ADVERSE REACTIONS: Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates.

The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedicants, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient.

The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency.

Incidence Greater than 1% – All events regardless of causality, derived from clinical trials

Body as a Whole: Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY), Bradycardia, Hypertension. **Central Nervous System:** Movement,* Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea,** Vomiting,* Abdominal Cramping. **Injection Site:** Burning/Stinging,** Pain,** Tingling/Numbness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing.

DIPRIVAN® (propofol) Injection

Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater.

Incidence Less than 1% – Causal Relationship Probable (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Body as a Whole: Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, *Green Urine.*

Incidence Less than 1% – Causal Relationship Unknown (Adverse events reported only in the literature, not seen in clinical trials, are *italicized.*)

Cardiovascular: Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, *Heart Block, Myocardial Ischemia.* **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, *Opisthotonus.* **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, *Conjunctival Hyperemia.* **Special Senses:** Ear Pain, *Nystagmus.* **Urogenital:** Abnormal Urine.

DRUG ABUSE AND DEPENDENCE: None known.

DOSAGE AND ADMINISTRATION: Induction: Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia.

It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See PRECAUTIONS, and DOSAGE GUIDE.)

Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction.

Maintenance: Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections.

When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates.

Continuous Infusion: DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%- 50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses.

For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile.

Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times.

Intermittent Bolus: Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia.

DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia, such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See Drug Interactions.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. **Adults:** Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	**Variable rate infusion** – titrated to the desired clinical effect. **Adults:** Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). **Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients:** Generally, 0.05 to 0.1 mg/kg/min (3 to 6 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration.

Dilution Prior to Administration: When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic.)

Administration Into a Running IV Catheter: Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See WARNINGS.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter.

- –5% Dextrose Injection, USP
- –Lactated Ringers Injection, USP
- –Lactated Ringers and 5% Dextrose Injection
- –5% Dextrose and 0.45% Sodium Chloride Injection, USP
- –5% Dextrose and 0.2% Sodium Chloride Injection, USP

Handling Procedures: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Do not use if there is evidence of separation of the phases of the emulsion.

Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms.

DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should then commence without extended delay.

DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection or solutions containing DIPRIVAN Injection must be discarded at the end of the surgical procedure.

Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness.

Rev. X 06/90

Made in Sweden
Manufactured for:
STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

Mock Orals Help Dr. Smith

Why the Osler course best meets your individual needs:

Home-study, lectures, and practice oral exams — limited to 90 participants

The *Osler Institute* Anesthesiology Oral Boards Tutorial

April 15-23, 1991 — San Diego

July 6-11, 1991 — Chicago Sept. 30-Oct. 5 — Tampa

Dear Fellow Physician:

Dr. Smith (not his real name) had failed his oral boards several times. His group was satisfied with his work but his job depended on becoming board certified. He was eligible to take the exam only one more time. A friend advised him to take our Osler Institute's Anesthesiology Board Review Course.

Home Study Questions

Before the course, we sent him several hundred pages of multiple choice questions and keywords with answers and explanations. These were given to us by past participants. Now we also have a collection of mock-oral-exam stem cases and related questions to send you.

Free Sample Offer

We offer to send you a gift without obligation: a free sample of our multiple choice questions or our mock oral cases. We would like to share these with you whether or not you take our course. Please request on course registration form.

Complete Syllabus

We can also send you a copy of a previous course syllabus. Our price to you is $60 (about our production cost). The supply is limited. Those registering for the six day lecture course will receive several hundred pages of current lecture notes and all home study materials at no extra charge.

Great Lectures

At the course, Dr. Smith enjoyed six days of outstanding lectures by some of the best-known teachers in anesthesiology — as well as by several outstanding junior faculty who had been asked back because of their excellent participant evaluation scores. Also several new faculty had been recommended for their speaking ability.

Some of the lectures were of little use to Dr. Smith — he is regarded as an expert in his field; he could have given several of the lectures himself. Knowledge was not his problem; his problem was presenting his knowledge in the oral exam. He skipped several lectures to attend:

Mock Oral Exams

The first day of the course, a recently retired board examiner explained the philosophy, process, and scoring of the real oral exam. Each evening as well as concurrent with most lectures there were mock oral exams for Dr. Smith. These are group sessions with one participant taking the hot seat for about 25 minutes while others watch. Each participant is entitled to a turn in the hot seat as well as unlimited observation of others.

When Dr. Smith took the hot seat his heart quickened, his palms sweated, and his hands shook. The faculty presented a stem question, paused a minute, then asked the first question. Dr. Smith opened his mouth, but his tongue was thick and dry. He stammered and stuttered — failed to form even a sentence — just like when he failed the real oral exam. But this time was different; the faculty coached and encouraged him. His panic passed and his performance improved.

Extra Mock Orals

The course budget could not support enough faculty for an unlimited number of mock orals for every participant. In our previous course, assertive attendees had taken the hot seat repeatedly before others had a chance. In response, we mark participant name tags for the first mock oral. We also hire additional faculty time and sell $70 tickets for extra turns in the hot seat.

Dr. Smith became more comfortable in the hot seat. He continued to improve.

Private and Dual Orals

Dr. Lee, however, was too shy to take the hot seat in front of anyone else. We now have a thirty dollar surcharge for private sessions. Also, Dr. Jones wanted two examiners, just like the real exam. Such sessions take twice the faculty time, so we must charge $140 per session.

Video Mock Orals

At our June course, we had a portable TV studio to make educational tapes with some of the faculty. Video taping mock orals was so popular that we now offer a video tape of your practice exam for an extra ten dollars per session.

Extra Mock Oral Days

Lectures end on Saturday and the real oral exams are the next Monday through Friday. What do you do in the meantime? Sunday through Tuesday of oral exam week are optional extra days of mock oral exams. For $140 per day, attendees receive one 25 minute hot seat session and observation of other sessions for nine hours.

Your Individual Needs

The quality of our courses gave us growth. Growth helped us improve to meet your individual needs. At the course, you may choose every hour between a lecture or observation of one-on-one mock oral exams.

Passing Your Boards

Will our course help you pass your boards? Dr. Smith passed his oral exam the week after our course. A candidate calling to register for our course told us:

> *"Five of my partners took your course; they all passed their oral boards; and they all recommended your course."*

One of our faculty reported:

> *"All of my residents who took the course passed their boards."*

We can't guarantee that you will pass. We can't say that taking our course will make the difference between passing or failing. All we can say is that a lot of our participants tell us that the course was helpful. See registration form to request a free sample.

We look forward to meeting you at our course and helping you to pass your board exams.

Cordially,

Joe Sellike

Joseph H. Selliken, Jr., M.D.

P.S. To reserve your place call today

(800) 356-7537

***Limited Enrollment*: Anesthesiology Tutorial Registration**

Name ______________________________

Address ______________________________

City/State/Zip ______________________________

Phone ______________________

For: ☐ Apr. 15-23, 1991 — San Diego
☐ July 6-11, 1991 — Chicago
☐ Sept. 30-Oct. 8 — Tampa

Mail Today to:

1094 Dawn Lane, Dept. A14
P.O. Box 2218
Terre Haute, IN 47802

☐ Check Enclosed for $______
☐ Please send free sample

28th ANNUAL

NEW YORK ANESTHESIOLOGY REVIEW

June 17-21, 1991
Waldorf Astoria Hotel
New York City

ALBERT EINSTEIN
COLLEGE OF MEDICINE/
MONTEFIORE
MEDICAL CENTER
AND
MOUNT SINAI
MEDICAL CENTER

FOCUS

The 28th Annual New York Anesthesiology Review provides a comprehensive and integrated study of current practice that prepares participants for successful performance on both the 1991 Written and Oral Board Examinations. This program also provides a thorough up-date for the practicing anesthesiologist emphasizing the latest pharmacologic and technologic advances in the field.

FORMAT

GENERAL SESSIONS: Each day, all registrants meet in general session for six or seven presentations followed by questions and discussion (32 presentations over five days). Presentations focus on the seminal topics in anesthesia, conducted by acknowledged leaders in the field.

KEY-WORD REVIEWS: Following each General Session (Mon. - Thurs.) participants attend group discussions, team-taught by faculty from the Albert Einstein College of Medicine, and designed specifically for anesthesiologists working toward the written board examination.

BREAKFAST MEETINGS: In addition, faculty from the host institutions offer participants both small-group meetings covering case discussions and Special Workshops that explore the management of specific situations.

GUEST FACULTY
Paul G. Barash, M.D.
Philip O. Bridenbaugh, M.D.
D. Ryan Cook, M.D.
Edmond I. Eger II, M.D.
Burton S. Epstein, M.D.
Mieczyslaw Finster, M.D.
Edward D. Miller, M.D.
Ronald D. Miller, M.D.
Barry A. Shapiro, M.D.
Richard M. Sommer, M.D.
Paul F. White, M.D.

HOST FACULTY
Albert Einstein
College of Medicine/
Montefiore Medical Center
and
Mount Sinai Medical Center

DIRECTOR
Elizabeth A.M. Frost, M.D.

CO-DIRECTORS
Paul L. Goldiner, M.D., D.D.S
Joel A. Kaplan, M.D.

REGISTRATION FORM

Please register me for THE 28th ANNUAL NEW YORK ANESTHESIOLOGY REVIEW to be held at the Waldorf Astoria Hotel on Monday-Friday June 17-21, 1991

Name ....
Address ....
City .... State .... Zip ....
Telephone (day) ....

Please Check:	☐ **Attending M.D.**	☐ **Resident**	☐ **CRNA**
FEE:	$495.00	$395.00	$395.00

Please make checks payable to **"CONTINUING MEDICAL EDUCATION"**

Mail to **Office of Continuing Medical Education**
Albert Einstein College of Medicine / Montefiore Medical Center
3301 Bainbridge Avenue / Bronx, New York 10467

FOR FURTHER INFORMATION
(212) 920-6674

Anesthesiology Review Seminar

Sponsored by Creighton University School of Medicine and Professional Seminars, Inc

April 15-22, 1991 San Diego

Unlimited Mock Oral Practice Sessions

Creighton University and Professional Seminars, Inc. present an intensive review seminar intended for practicing physicians needing to fulfill their **CME requirements** and candidates preparing to take their **oral or wirtten board exam.** Emphasizing fundamental principles and clinical practice, lectures will reflect the leading edge of current techniques and research.

The faculty selected for the Anesthesiology Review Seminar are among the best teachers on the lecture circuit today. Involved in spearheading new research and discovery, they provide participants with **fresh perspective and enthusiasm** as well as a current knowledge base.

Daily mock oral sessions give individual attention to each participant. Practice examiners will help polish your presentation by teaching you thought organization and delivery. **Special sessions** are scheduled to teach you the *do's* and *don'ts* of taking the oral exam and to explain how the actual exam is scored.

Home study material is available upon request to enable candidates to focus on areas needing attention at the course.

Attendance at this seminar **will be kept low** to enable faculty and staff to attend to the individual needs of each participant. Only the **first 100** registrations will be accepted.

For a complete list of **topics, faculty or references**, call Professional Seminars, Inc. at 1-800-445-4564 or wirte to P.O. Box 498, Clinton, IN 47842. To register for this course,call Creighton University, CME Division at 1-800-548-2633.

*"Your **limited registration** was definitely a plus. It gave me the opportunity to work individually with the faculty and **made me more relaxed** about the upcoming exam."*

*"Participating in the mock orals gave me the **practice and confidence** I **needed.** After your course, I felt prepared..."*

*"Attending your course **just before** my exam was the best thing I could have done to prepare for my actual exam.I passed on my **first try**. I will recommend it to my associates."*

Creighton University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Creighton University School of Medicine designates this continuing medical education activity for **60 hours in Category 1** of the Physicians Recognition Award of the American Medical Association. One credit hour may be claimed for each hour of participation by physicians.

Name ____________
Address ____________
City/St/Zip ____________
Phone ____________
Social Security # ____________
Visa/Mastercard ____________ exp. ____________

$675 - San Diego April 15-20
$120/day-extra mock orals Apr. 21,22
$450 - repeating or residents
Pay to: Professional Seminars, Inc.
Mail to: Creighton University
Division of CME
California at 24th Street
Omaha, NE 68178

TRACRIUM®

Easy reversal, complete recovery

Rapid elimination of Tracrium means easy reversal and fast, complete recovery. Of all the agents in its class,* Tracrium has the shortest elimination half-life (approx. 20 min.).[1]

Low risk of residual blockade

In short and long procedures and in a wide range of patient types, its unique metabolism — unaffected by renal or hepatic dysfunction — gives Tracrium the most consistent pharmacodynamic profile of any nondepolarizing neuromuscular blocker.[2]

Outstanding record of cardiovascular safety

Documented by two recent surveillance studies: "The absence of a significant difference in cardiovascular events between the atracurium and comparison groups in the U.S. study was corroborated in the U.K. study; however in the latter, the vecuronium group experienced more cardiovascular events than the atracurium group."[3]

*Nondepolarizing neuromuscular blocking agents.

TRACRIUM® INJECTION

(atracurium besylate)

References and brief summary of full prescribing information can be found on the following page.

TRACRIUM® INJECTION
(atracurium besylate)

Ready-to-use convenience, stable 14 days on carts and trays

Brief Summary
This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Observed in Controlled Clinical Studies: Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if rerefrigerated.

---

1. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. *Anesthesiology.* 1984;61:444-453.
2. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). *Br J Anaesth.* 1983;55:1169-1172.
3. Lawson DH, Paice GM, Glavin RJ, et al. Atracurium — a post-marketing surveillance study: U.K. study and discussion. *Br J Anaesth.* 1989;62:596-600.

Wellcome
Burroughs Wellcome Co.
Research Triangle Park, NC 27709
Copr. © 1990 Burroughs Wellcome Co. All rights reserved.
TR-476

An Invaluable Source for Neurologists and Neurosurgeons

Focal Peripheral Neuropathies

John D. Stewart, B.Sc., M.B., B.S., M.R.C.P., F.R.C.P.(C),
Associate Professor, Department of Neurology and Neurosurgery and Department of Medicine, McGill University; Director EMG Laboratory, The Montreal General Hospital, Montreal, Quebec

Illustrated by **Margo Siminovitch, B.Sc., A.A.M.,**
Director of Educational Resources, The Montreal General Hospital, Montreal, Quebec

"... successfully fills a gap left by others in the field ... tested the book in the field ... seldom did it fail to come up with a useful teaching or practice point ... Neurologists, neurosurgeons, physiologists, and orthopedic surgeons should buy this book." – *Neurology*

This 421 page, 24 chapter text is devoted to the study of lesions of the individual peripheral nerves, from the spinal nerve roots to the terminal digital branches. The text systematically discusses the causes, symptoms, and differential diagnoses of radiculopathies, plexopathies, and focal neuropathies involving individual peripheral nerve trunks and their more important branches.

1987 • 421 pages • 117 figures • cloth • 0-444-01132-3 • $67.50
(Dfl. 205.00 outside North America)

Contents

1 The Structure of the Peripheral Nervous System
2 Pathological Process Producing Focal Peripheral Neuropathies
3 Electrical Activity in Normal and Abnormal Nerves
4 The Evaluation of Patients with Focal Neuropathies
5 The Cervical Spinal Nerve Roots and Spinal Nerves
6 The Cervical Plexus and the Nerves of the Neck
7 The Brachial Plexus
8 The Nerves Arising from the Brachial Plexus
9 The Median Nerve
10 The Ulnar Nerve
11 The Radial Nerve
12 The Digital Nerves
13 The Cauda Equina, Lumbar and Sacral Nerve Roots, and Spinal Nerves
14 The Lumbosacral Plexus
15 The Sciatic Nerve, the Gluteal and Pudendal Nerves, and the Posterior Cutaneous Nerve of the Thigh
16 The Common Peroneal Nerve
17 The Tibial, Plantar, Interdigital, and Sural Nerves
18 The Femoral and Saphenous Nerves
19 The Lateral Cutaneous Nerve of the Thigh
20 The Obturator Nerve
21 The Iliohypogastric, Ilioinguinal, and Genitofemoral Nerves
22 The Thoracic Spinal Nerves
23 Mononeuropathy Multiplex
24 Neuropathic Pain

Order from your usual supplier or:

In North America
Elsevier Science Publishing Co., Inc.
Box 882, Madison Square Station
New York, New York 10159

Outside North America
Elsevier Science Publishers
Box 211
1000 AE Amsterdam
The Netherlands

For Faster Service, call or fax today to place your order:
Telephone #: (212) 633-3650
Fax #: (212) 633-3880

ELSEVIER SCIENCE PUBLISHING CO., INC.
655 Avenue of the Americas, New York, NY 10010

X6AP

7/90

If You're Looking For The Best Anesthesiology Billing and Practice Management System, We've Got Your Number.

1-800-2GET-NHS

Call us today, and we'll send you a free information kit on the best computer system designed exclusively for anesthesiologists —The ULTRA Anesthesiology Billing and Practice Management System from Northern Health Systems.

You'll receive all of the information you need to automate your growing practice.

Information that will improve the efficiency of your office and speed your cash flow.

You'll discover a feature-packed system that can give you instant patient information. Simplify your accounting. Process your claims electronically. Produce customized reports. And much, much more.

Call us toll-free at 1-800-2GET-NHS for your free information kit. It's the only number you need.

NHS ***Northern Health Systems, Inc.***
5500 Corporate Drive, Pittsburgh, PA 15237

How to talk about drug abuse in the presurgical interview

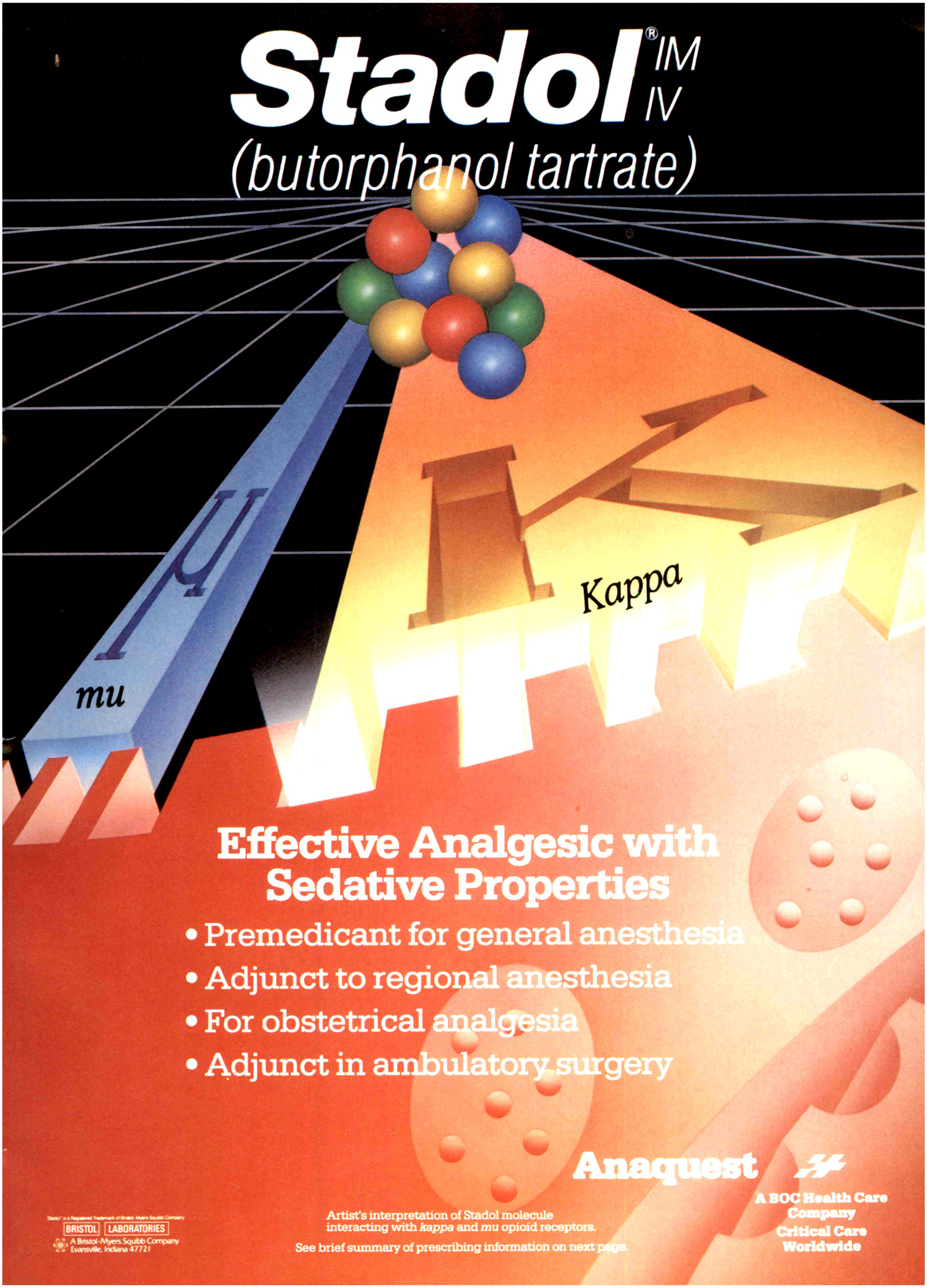
ASK your patients if they use illegal drugs. Explain the possible effects of interactions with OR medications, and the long-term health risks of drug abuse.

LOOK for signs of drug abuse: avoidance of eye contact, increased motor activity, compulsive behavior, extreme nervousness, or dilation of the pupils.

LISTEN closely for answers such as "Well, I do drugs sometimes."

JUDGE NOT. Be candid and forthright, and not condescending, and you will encourage your patients to be honest.

PARTNERSHIP FOR A DRUG-FREE AMERICA



Stadol® IM IV
(butorphanol tartrate)

Effective Analgesic with Sedative Properties

- Premedicant for general anesthesia
- Adjunct to regional anesthesia
- For obstetrical analgesia
- Adjunct in ambulatory surgery

Anaquest
A BOC Health Care Company
Critical Care Worldwide

Stadol® is a Registered Trademark of Bristol-Myers Squibb Company
BRISTOL LABORATORIES
A Bristol-Myers Squibb Company
Evansville, Indiana 47721

Artist's interpretation of Stadol molecule interacting with *kappa* and *mu* opioid receptors.

See brief summary of prescribing information on next page.

Stadol® *(butorphanol tartrate)*

For complete information consult official package circular.

INDICATIONS AND USAGE

Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS

Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS

Patients Physically Dependent on Narcotics

Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Use During Balanced Anesthesia

Since the combined respiratory depressant effect of all intravenous medication used during conduct of general anesthesia may lead to underventilation or apnea, butorphanol should be administered during balanced anesthesia only by persons specifically trained in the use of intravenous anesthetics and adjuncts, the maintenance of a patent airway and management of respiratory effects of all intravenous medication administered.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

Drug Dependence

Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure

Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects

Because Stadol increases the work of the heart, especially the pulmonary circuit, (see Clinical Pharmacology), the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS

Certain Respiratory Conditions

Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function

Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery

Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Pre-operative or Pre-anesthetic Medication

Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Pregnancy

The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice, and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery

In general, the safety to the mother and fetus following the administration of Stadol during labor has been established, however, there have been a few reports of infant respiratory distress/apnea occurring after delivery (less than 1%; see Adverse Reactions). Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers

The use of Stadol in lactating mothers who are nursing their infants is not recommended, since it is not known whether this drug is excreted in milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children

Safety and efficacy in children below age 18 years have not been established at present.

ADVERSE REACTIONS

The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations, seizures

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: Vomiting

Respiratory: slowing of respiration, shallow breathing, apnea

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE

Manifestations

Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment

The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

SUPPLY

Stadol (butorphanol tartrate Inj., USP) for I.M. or I.V. use is available as follows:
NDC 0015-5644-20 - 2 mg per mL, 2-mL vial
NDC 0015-5645-20 - 1 mg per mL, 1-mL vial
NDC 0015-5646-20 - 2 mg per mL, 1-mL vial
NDC 0015-5648-20 - 2 mg per mL, 10-mL multi-dose vial

For information on package sizes available, refer to the current price schedule.

BRISTOL LABORATORIES
Bristol-Myers
U.S. Pharmaceutical and Nutritional Group
Evansville, Indiana 47721

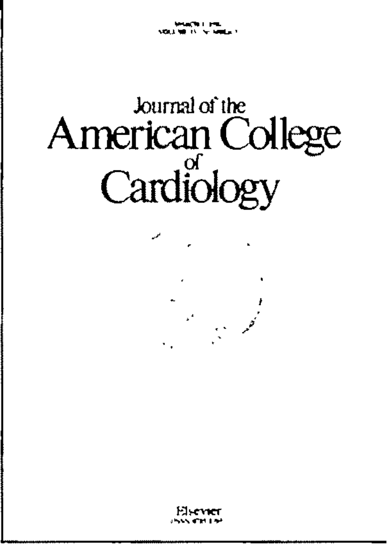
Follow the Leader in Cardiology

Read JACC monthly

Journal of the American College of Cardiology

The **Journal of the American College of Cardiology, JACC,** is the leading journal in cardiology. **JACC's** timely coverage of clinically relevant information on the diagnosis and treatment of cardiovascular diseases has made it a favorite among cardiologists worldwide.

Why not join the thousands of your colleagues who have made reading **JACC** a part of their regular routine?



Journal of the American College of Cardiology

Elsevier

Read the **Journal of the American College of Cardiology** each month and you will find a superb collection of original articles, clinical reviews, special reports, and editorials at the forefront of cardiovascular medicine. **JACC's** comprehensive focus and distinguished editorial board assure you the most significant new information—information that you can apply directly to your practice.

Discover why **JACC** is the #1 journal in cardiology. Enter your subscription today and follow the most current and authoritative source on important developments in cardiology.

Journal of the American College of Cardiology
Volumes 17, 18 (14 issues + 1 supplement)
ISSN 0735-1097

Personal Rate: $88.00*
Institutional Rate: $132.00
Intern/Resident Rate: $55.00†

Subscribers in the U.S., Canada, or Mexico may request air delivery for an additional $115.00. Subscribers outside the U.S. must add one of the following postage options: $60.00 (surface delivery); $160.00 (surface air lift/Europe); $210.00 (surface air lift/Japan); or $305.00 (air/rest of world).

Note: All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Please allow 4-6 weeks for delivery of your first journal issue. Subscription rates valid until December 31, 1991.

*The personal rate is available to individuals only. A home, hospital or medical school address must be used for delivery. Orders from non-U.S. customers must be prepaid.

† Intern/Resident Rate is valid for two years only. Please send proof of status.

For sample copies send to:
in North America: Elsevier
Science Publishing Co., Inc.,
P.O. Box 882,
Madison Square Station
New York, New York 10159
in the rest of the world:
Elsevier Science Publishers,
Direct Mail Department
P.O. Box 211, 1000 AE
Amsterdam, The Netherlands

ELSEVIER
SCIENCE PUBLISHING
COMPANY, INC.

Send subscription orders to your usual supplier or the New York address. For even faster service, call
(212) 633-3950 or f
(212) 633-3880

X7AQ
9/90
BIAE04SA

- Original papers
- Editorials and Editorial Notes
- Brief Reports
- Reviews

International Journal of CARDIOLOGY

Informative - Controversial - A Truly International Journal

EDITORS

ROBERT H. ANDERSON, National Heart & Lung Institute, Dovehouse Street, London SW3 6LY, UK MICHAEL TYNAN, Guy's Hospital, St. Thomas Street, London SE1 9RT, UK CHUICHI KAWAI, Third Division, Department of Internal Medicine, Kyoto University Hospital, 54 Kawaracho Shogoin, Sakyo-ku, Kyoto 606, Japan ROBERT L. FRYE, Department of Internal Medicine, The Mayo Clinic, 200 1st Street S.W., Rochester, MN 55905, USA; RAYMOND GIBBONS and BERNARD GERSH, Department of Cardiovascular Diseases, The Mayo Clinic, 200 1st Street S.W., Rochester, MN 55905, USA

SCOPE

The *International Journal of Cardiology* is devoted to cardiology in the broadest sense. Both basic research and clinical papers may be submitted, but articles on the fundamental principles of cardiology will also be considered for publication. The journal serves the interest of both practicing clinicians and research workers. Editorials, Brief Reports and Review Articles covering recent developments are included. Controversial techniques, issues on Health Policy and Social Medicine are discussed and serve as useful tools for encouraging debate.
The *International Journal of Cardiology* covers the fields listed below.

EDITORIAL BOARD

Cardiovascular Research
Allen Cowley Jr., Milwaukee, U.S.A.
David A.S.G. Mary, Leeds, U.K.
Winifred Nayler, Melbourne, Australia
Gabor Rubanyi, Rochester, MN, U.S.A.
Thomas W. Smith, Boston, U.S.A.
Michihiko Tada, Osaka, Japan

Cardiac Catheterization and Invasive Techniques
David Faxon, Boston, U.S.A.
M. Kaltenbach, Frankfurt Am Main, F.R.G.
Carl Pepine, Gainesville, U.S.A.
Peter Rentrop, New York, U.S.A.
Shigetake Sasayama, Toyama, Japan

Cardiology in the Young
Valmir F. Fontes, Sao Paulo, Brazil
Robert M. Freedom, Toronto, Canada
Edward L. Kaplan, Minneapolis, U.S.A.
Douglas S. Moodie, Cleveland, U.S.A.
Norman H. Silverman, San Francisco, U.S.A.
Madison S. Spach, Durham, U.S.A.
James L. Wilkinson, Parkville, Australia

Cardiovascular Surgery
Philip B. Deverall, London, U.K.
G. Kaiser, St. Louis, U.S.A.
Guillermo Kreutzer, Buenos Aires, Argentina
Fernando A. Lucchese, Porto Alegre, Brazil
Bruce A. Reitz, Baltimore, U.S.A.

Clinical Cardiology
Fulvio Camerini, Trieste, Italy
Douglas A. Chamberlain, Brighton, U.K.
David P. de Bono, Edinburgh, U.K.
Henri Denolin, Brussels, Belgium
Gottlieb C. Friesinger, Nashville, U.S.A.
Valentin Fuster, New York, U.S.A.
Clive E. Handler, London, U.K.
K.I. Lie, Groningen, The Netherlands
Bernard Lown, Boston, U.S.A.
Lars Mogensen, Stockholm, Sweden
Matoomi Nakamura, Fukuoka, Japan
Paul J. Oldershaw, London, U.K.
Robert A. O'Rourke, San Antonio, U.S.A.
Aubrey Pitt, Prahran, Australia
Edward B. Raftery, Harrow, U.K.
Norman Sharpe, Auckland, New Zealand
Desmond Sheridan, London, U.K.
James T. Willerson, Houston, U.S.A.

Electrophysiology
Rodney S. Bexton, Newcastle, U.K.
Felix I.M. Bonke, Maastricht, The Netherlands
Nancy C. Flowers, Augusta, U.S.A.
J. Warren Harthorne, Boston, U.S.A.
Ralph Lazzara, Oklahoma City, U.S.A.
Erik Orinius, Stockholm, Sweden
Edgar Sowton, London, U.K.
Yoshio Watanabe, Toyoake, Aichi, Japan

Hypertension
William A. Littler, Birmingham, U.K.
Teruo Omae, Suita, Japan
Robert G. Wilcox, Nottingham, U.K.
Yukio Yamori, Izumo, Japan

Imaging
George A. Beller, Charlottesville, U.S.A.
Derek Gibson, London, U.K.
Gerald M. Pohost, Birmingham, U.S.A.
Nathaniel Reichek, Philadelphia, U.S.A.
Joseph R.T.C. Roelandt, Rotterdam, The Netherlands
Martin G. St. John Sutton, Boston, U.S.A.
A. Jamil Tajik, Rochester, MN, U.S.A.

Pathology
Anton E. Becker, Amsterdam, The Netherlands
Gaetano Thiene, Padua, Italy
Bruce F. Waller, Indianapolis, U.S.A.

Pharmacology
J. Thomas Bigger, Jr., New York, U.S.A.
Kanu Chatterjee, San Francisco, U.S.A.
Joseph A. Franciosa, East Rutherford, U.S.A.
Udho Thadani, Oklahoma, U.S.A.
Hisakazu Yasuda, Sapporo, Japan

Epidemiology and Biostatistics
Henry Blackburn, Minneapolis, U.S.A.
Eugene H. Blackstone, Birmingham, U.S.A.
Lila Elveback, Rochester, MN, U.S.A.
Paul Meier, Chicago, U.S.A.

CONSULTING EDITOR

Howard B. Burchell, Minneapolis, U.S.A.

Cited/abstracted in: Current Contents (Life Sciences; Clinical Medicine), Excerpta Medica (EMBASE), Index Internacional de Cardiologia; Index Medicus (MEDLINE)

SUBSCRIPTION INFORMATION

1991: Volumes 30-33 (4 volumes in 12 issues)
Institutional Rate: Dfl. 1304.00/US$ 652.00
A Personal Rate is available - apply to the Publisher for details. Prices **include** postage and handling.
ISSN 0167-5273

ELSEVIER

For further information and/or FREE SAMPLE COPY please write to:

In the U.S.A. and Canada:
ELSEVIER SCIENCE PUBLISHING CO., INC.,
P.O. Box 882, Madison Square Station,
New York, NY 10159, U.S.A.

In all other countries:
ELSEVIER SCIENCE PUBLISHERS
P.O. Box 211, 1000 AE Amsterdam,
The Netherlands.

Please send your orders to the Amsterdam address.
A given Dutch guilder price is definitive. Prices are excl. B.T.W. for Dutch customers.

01-103/dtpgvl/0690/074

Columbia University

DIRECTOR

Department of Anesthesiology

Harlem Hospital Center, a 672-bed, full service, acute care hospital and a major teaching affiliate of the Columbia University College of Physicians and Surgeons, seeks a full time Director for the Dept. of Anesthesiology. The Dept. serves an active Operating Theater and related support functions, and provides training for our accredited school for Certified Nurse Anesthetists.

Candidates should have expertise and board certification in Clinical Anesthesiology, must qualify for senior academic appointment at the Professor/Associate Professor level, and must have established teaching and administrative abilities.

A competitive salary commensurate with qualifications and excellent benefits are provided. Please address correspondence to: Sterling B. Williams, MD, Chairman, Anesthesiology Search Committee, Harlem Hospital Center, MLK Pavilion Room 4139, 506 Lenox Avenue, New York, NY 10037. Columbia University takes affirmative action to ensure equal opportunity.

Harlem Hospital Center
A Member of N Y C
Health and Hospitals Corp

IARS

NEW OFFICE ADDRESS

Effective October 1, 1990, the **International Anesthesia Research Society** headquarters office in Cleveland moved to the following new address:

International Anesthesia
Research Society
Suite 140, 2 Summit Park Drive
Cleveland, Ohio 44131-2553

NEW TELEPHONE NUMBER:
(216) 642-1124

All membership payments and correspondence regarding **IARS** member subscriptions, annual scientific meeting matters, the B.B. Sankey Anesthesia Advancement Award, etc., should be sent to the above address.

Pediatric Anesthesiologist

Pediatric Anesthesiologist needed for growing department in a pediatric referral center in Boston. Opportunity to participate in medical student and resident education. Interest in clinical research desirable.

Franciscan Children's Hospital conducts programs providing acute care and rehabilitation services including an inpatient Pediatric Ventilator Dependent program. The National Birth Defects Center is affiliated with and located at the Hospital.

Interested applicants should send CV to: Joseph J. Frassica, M.D., Director, Department of Anesthesia, Franciscan Children's Hospital and Rehabilitation Center, 30 Warren Street, Boston, MA 02135-3680.

An equal opportunity employer.

FRANCISCAN CHILDREN'S
H·O·S·P·I·T·A·L

ANESTHESIOLOGY

Board Certified/Eligible Anesthesiologist needed as Associate in Section of Anesthesia of 215 member multi-specialty clinic which serves as a referral center for surrounding areas of Northeastern Pennsylvania and the Southern Tier of New York State.

State-of-the-art facility. Medical school teaching affiliation through surgical residency program provides a stimulating environment. Tertiary Care Center performing 10,000 anesthetic procedures per year. Most types of surgery performed with emphasis on cardiovascular and neurosurgery.

Area provides attractive living conditions and many summer and winter recreational activities readily available. Easy access to major metropolitan areas. Excellent salary and fringe benefits. Respond with curriculum vitae to:

Guthrie Clinic
Sayre, PA 18840
(717) 888-5858

ATTN: G. V. Ippolito
Vice President

The Osler Institute

Anesthesiology Boards Review Course

§April 15-20, 1991 – San Diego

July 6-11, 1991 – Chicago §Sept. 30-Oct. 5, 1991 – Tampa

Now offering §60 hours of mock oral exams limited to 90 participants

Co-sponsored by the University of Washington

OBJECTIVES

After this program attendees should:
- Have improved basic and clinical anesthesia knowledge
- Be better organized for further study of anesthesiology
- Be prepared to take written and oral exams

METHODS
- HOME STUDY MATERIALS consisting of a syllabus and assignments with questions and answers
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."**

PHYSIOLOGY
- Respiratory Physiology
- Cardiovascular Physiology
- Neurophysiology
- Hepatic Physiology
- Renal Physiology
- Acid-Base and Blood Gas
- Endocrine Physiology
- Thermoregulation

PHARMACOLOGY
- Pharmacokinetics
- Inhalation Anesthetics
- Intravenous Anesthetics
- Muscle Relaxants
- Autonomic Drugs
- Central Nervous Drugs
- Cardiac & Diuretic Drugs
- Interactions & Genetics

PHYSICAL SCIENCES
- Applied Anatomy
- Physics and Gas Laws
- Anesthesia Machines
- Instrumentation
- Monitors and Ventilators
- Breathing Systems
- Defibrillators and Pacers

FUNDAMENTALS
- Preop. Evaluation & Prep.
- Patient Monitoring
- Airway Management
- Fluid and Blood Therapy
- Cardiopulmonary Disease
- Hepatic & Renal Disease
- Metabolic Disease
- Recovery Room

REGIONAL ANESTHESIA
- Local Anesthetics
- Autonomic Blocks
- Spinal and Epidural Blocks
- Caudal Blocks
- Upper Extremity Blocks
- Lower Extremity Blocks
- Chronic Pain Management

SPECIALTY AREAS
- Obstetric Anesthesia
- Pediatric Anesthesia
- Cardiac Anesthesia
- Thoracic Anesthesia
- Neuroanesthesia
- Ophthalmic & E.N.T.
- Geriatric and Outpatients
- Critical Care

FACULTY

Ezzat Abouleish, M.D.
U. of TX Med. Sch., Houston

Jonathan Benumof, M.D.
U. of California, San Diego

T. A. Bowdle, M.D., Ph.D.
University of Washington

Floyd Brauer, M.D.
Loma Linda University

Stan Brauer, M.D.
Loma Linda University

Burton Briggs, M.D.
Loma Linda University

Daniel Cole, M.D.
Loma Linda University

Hernando DeSoto, M.D.
Riverside Hosp., Jacksonville

John Drummond, M.D.
U. of California, San Diego

Richard Engel, M.D.
Escondido, California

Christopher Gallagher, M.D.
Anes. Services, San Diego

Richard Hanberry, M.D.
Lawrenceville, Georgia

Carl Hess, M.D.
Univ. of California, Irvine

Niels Jensen, M.D.
University of Iowa

David Lubarsky, M.D.
Duke University

Terence Murphy, M.D.
University of Washington

Danae Powers, M.D.
Emory University

Michael Ritter, M.D.
St. Louis University

David Rothenberg, M.D.
Rush Medical School

Amira Safwat, M.D.
University of California, Davis

Daniel Siker, M.D.
Medical College of Wisconsin

Kelly Smith, M.D.
University of Utah

Horace Spiess, M.D.
University of Washington

Ngoc-Hai Truong, M.D.
Fountain Valley, California

John Viljoen, M.D.
Univ. of Southern California

K.C. Wong, M.D.
University of Utah

Limited Enrollment: ANESTHESIOLOGY REVIEW COURSE REGISTRATION

Name ____________________

Address____________________

City/State/Zip____________________

Phone ____________________

Mail today to:

1094 Dawn Lane, Dept. 14A
P.O. Box 2218
Terre Haute, IN 47802

For: ☐ April 15-20, 1991 – San Diego
☐ July 6-11, 1991 – Chicago
☐ Sept. 30-Oct. 5, 1991 – Tampa
☐ Check enclosed for $________
☐ Please send more information

*"I feel [the course] helped me pass...."**

PROGRAM: This course is designed to prepare you for your board exams. Upon registration we will send you our home study material. At the course, one-on-one mock oral exams are held concurrent with most lectures. Each participant is assured a mock oral exam and observation of all non-private exams. You may reserve mock oral sessions at any course and optional extra days of mock oral exams — April 21-23. Past participants recommend repeating the course for half price just before your exams.

*"Accommodations were comfortable...."**

LOCATION: The April course will be at the San Diego Princess Resort in Mission Bay, 1404 West Vacation Road, San Diego, California.

*"...the most education for the money."**

FEES AND CATEGORY 1 C.M.E.:

• 6 day lectures and mock orals:	$660
Residents and Fellows fee:	$440
Repeating course within 3 years:	$330
• Mock oral observation only (6 day):	$400
Per day mock oral observation:	$ 70
• Single examiner mock oral exam:	$ 70
• Dual examiner mock oral exam:	$140
• Surcharge for private exam:	$ 30
• Surcharge for videotaped exam:	$ 10
• Previous course syllabus:	$ 60

- Attendees not in course hotel add $20/day.
- A deposit of $50 will reserve your position.
- Most home study materials will be mailed after half of the registration fee is received.
- Subject to a $50 fee, refunds will be made up until the seminar begins.
- The University of Washington School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians.
  The University of Washington School of Medicine designates this Continuing Medical Education activity for up to **90 credit hours** in **Category 1** of the Physician's Recognition Award of the American Medical Association.

*"...home study material was extremely helpful."**

INFORMATION:

1094 Dawn Lane, P.O. Box 2218
Terre Haute, IN 47802
(812) 299-5658 or

(800) 356-7537

* *Comments by past Osler participants*

§ Plus optional extra days Apr. 21-23 & Oct. 6-8.

"I was immediately impressed with the breadth of topics covered…
In order to evaluate the book as a reference text, I put it into service in our Drug Information Center for one month. We found answers to around 85 percent of our questions; those not found were candidates for searches of the primary literature, not a general reference work."
– DICP, The Annals of Pharmacotherapy

PHARMACOTHERAPY
A Pathophysiologic Approach

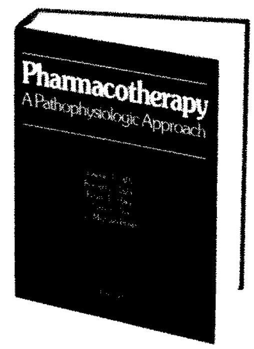
Edited by:
Joseph T. DiPiro, PharmD, University of Georgia
Robert L. Talbert, PharmD, University of Texas
Peggy E. Hayes, PharmD, Virginia Commonwealth University
Gary C. Yee, PharmD, University of Florida
L. Michael Posey, PAS Pharmacy/Association Services

By stressing the underlying pathophysiology, this outstanding reference is one of the most comprehensive texts available on pharmacotherapeutics – and an invaluable reference for the practicing physician. This superb text will be a *key* aid in choosing the best drug therapy for your patients. You'll have at your fingertips the expertise of over 150 highly regarded clinical pharmacists, helping you to understand the best strategies in rational drug therapy for *all* the major disease states.

"The listing of authors reads like a 'Who's Who' in clinical pharmacy."
– DICP, The Annals of Pharmacotherapy

This extensive volume of 1,730 pages includes in-depth sections on the pharmacological treatment of cardiovascular, respiratory, gastrointestinal, renal, neurologic, psychiatric, oncologic, and nutritional disorders. There is also an excellent section on infectious diseases, providing much needed information in this critical area. In addition, the book has specific chapters devoted to important adverse drug effects.

1989 1,730 pages cloth 0-444-01323-7 $89.50 (Dfl. 171.00 outside North America)



Pharmacotherapy
A Pathophysiologic Approach

Send orders to:
in North America:
Elsevier Science Publishing Co., Inc.
Attn: M. Fastiggi
Box 882, Madison Square Station
New York, NY 10159

in the rest of the world:
Elsevier Science Publishers
Direct Mail Department
Box 211
1000 AE Amsterdam
The Netherlands

For faster service, phone (212) 633-3650 or FAX (212) 633-3880.

Note: Price subject to change without notice

ELSEVIER 2/90 X4AJ

NEW– First Issue October 1990

An important new resource in epidemiology

ANNALS OF EPIDEMIOLOGY

Co-Editors-in-Chief: Charles H. Hennekens, MD, and Julie E. Buring, DSc, Brigham & Women's Hospital, Harvard Medical School, Boston, MA, USA

Annals of Epidemiology is a new international journal publishing reports of original research in the epidemiology of chronic and acute diseases for clinicians as well as public health researchers. The journal covers research on the distribution and determinants of the current leading causes of morbidity and mortality in both developed and developing countries, including:

- coronary heart disease
- cancer
- infectious diseases
- birth defects
- injuries
- stroke
- AIDS
- alcoholism & drug addiction
- diseases of aging
- respiratory diseases

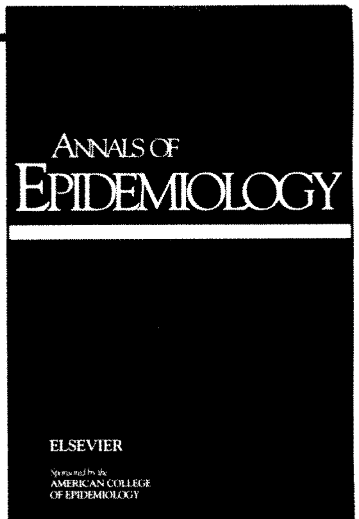
Sponsored by the *American College of Epidemiology*, **Annals of Epidemiology** is headed by an international editorial board bringing you the newest advances from around the world. **Annals of Epidemiology** features:

- *original reports* describing the results of new epidemiologic research
- *review articles* summarizing the current status of knowledge in important areas of epidemiology, either established or developing
- *specially selected proceedings* from various international symposia

In addition to these articles, **Annals of Epidemiology** is packed with pertinent information in the form of brief reports, methodologic issues involved in conducting epidemiologic research, editorials, and letters to the editor.

The primary focus of all articles is on new developments concerning issues of major importance in clinical medicine and public health.

Don't miss a single issue! Subscribe to this invaluable resource today.



ANNALS OF
EPIDEMIOLOGY

ELSEVIER

Sponsored by the
AMERICAN COLLEGE
OF EPIDEMIOLOGY

Subscription Information
Volume 1, 1990-91 (6 issues in one volume)
• ISSN 1047-2729 • Institutional Rate: $125.00 • Individual Rate: $85.00*
• Subscribers outside the U.S., please add $26.00 for postage & handling.
*Individual subscriptions must be paid by personal check or charge card.

Return subscription orders to: Elsevier Science Publishing Co., Inc. • Attn: S. Roberts • P.O. Box 882, Madison Square Station • New York, NY 10159

Send sample copy requests to: *In North America* • **Elsevier Science Publishing Co., Inc.** • Attn: Journal Information Center • P.O. Box 882, Madison Square Station • New York, NY 10159

Outside North America • **Elsevier Science Publishers** • P.O. Box 211 • 1000 AE Amsterdam • The Netherlands

For Faster Service, call or fax today to place your order:
Telephone #: (212) 633-3950 Fax #: (212) 633-3880

Note: All subscriptions begin with the first issue of the calendar year and are entered upon receipt of payment. Subscription rates valid through December 31, 1991. Please allow 6-8 weeks for delivery of the first issue.

ELSEVIER 9/90 X7A1 BISR003A

For surgical procedures
90 minutes or longer...

ARDUAN®

(pipecuronium bromide)
for injection

Long-acting muscle relaxation without vagolytic effects[1]

- Does not cause elevation of heart rate or blood pressure.[2]
- Recommended when cardiovascular stability is desired.[3]
- A useful alternative to pancuronium in patients where tachycardia is best avoided.[4]
- Provides good to excellent intubating conditions within 2.5 to 3.0 minutes.

See following page for brief summary of prescribing information.

Organon

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

ARDUAN®

(pipecuronium bromide)
for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known.
WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.
PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.
Renal Failure: ARDUAN®, in the dose of 70 μg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.
Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.
Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.
Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.
Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.
Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebration. Therefore, administration must be accompanied by adequate anesthesia.
Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.
Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.
Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.
Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.
Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 μg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 μg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.
Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a μg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED_{95}. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T_1 to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.
ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:
Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.
Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.
Musculoskeletal: muscle atrophy, difficult intubation.
Nervous: hypesthesia, CNS depression.
Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.
Skin and Appendages: rash, urticaria.
Urogenital System: anuria.
HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bromide and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-37)
Storage: 2°-30°C (36°-86°F). Protect from light.
After Reconstitution: When reconstituted with bacteriostatic water for injection, USP: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REFERENCES

1. Data on file.
2. Foldes FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. *Can J Anaesth.* 1990;37(5):549-555.
3. Lorijani GE, Bartkowski RR, Azad SS, et al. Clinical pharmacology of pipecuronium bromide. *Anesth Analg.* 1989;68:734-739.
4. Tassonyi E, Neidheart P, Pittet J-F, Morel DR, Gemperle M. Cardiovascular effects of pipecuronium and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology.* 1988;69(5):793-796.

ORGANON INC. WEST ORANGE, NEW JERSEY 07052

or by

BEN VENUE LABS., INC. BEDFORD, OHIO 44146
PTD. IN USA 446 6/90

ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

"® Registered Trademark; Licensed from the chemical works of Gedeon Richtor Ltd., Budapest, Hungary"

ORG-12370 © 1991 ORGANON INC. PRINTED IN USA MARCH 1991

Potentiation of Atracurium Neuromuscular Blockade by Enflurane: Time-Course of Effect

Davinia E. Withington, MB, FFARCS, François Donati, PhD, MD, FRCPC,
David R. Bevan, MB, MRCP, FFARCS, and France Varin, PhD

WITHINGTON DE, DONATI F, BEVAN DR, VARIN F. Potentiation of atracurium neuromuscular blockade by enflurane: time-course of effect. Anesth Analg 1991;72: 469–73.

This study was designed to determine the time required for potentiation of atracurium neuromuscular blockade after the introduction of enflurane. Ten ASA physical status I and II adults anesthetized with thiopental, nitrous oxide, and alfentanil were given 0.4 mg/kg atracurium besylate. The force of contraction of the adductor pollicis muscle in response to train-of-four stimulation of the ulnar nerve was recorded. When the first twitch (T1) of the train-of-four recovered to 10% of control, an atracurium infusion was started and adjusted to keep the level of blockade constant. After 15 min of stable blockade, 1.6%–1.7% end-tidal enflurane was started and maintained for up to 2 h. Venous blood samples were drawn and plasma atracurium concentrations were measured 15 min before and 0, 5, 10, 15, 30, 45, 60, 90, and 120 min after the introduction of enflurane. Atracurium plasma concentrations were 730 ± 127 (SEM) ng/mL at time 0. During the first 30 min, no significant decrease in plasma levels occurred; but at 45 min, concentrations were only 67% ± 8% of their initial value ($P < 0.01$) and 48% ± 2% at 120 min ($P < 0.01$). This suggests that the interaction between enflurane and atracurium is time-dependent. Clinically, the interaction between atracurium and enflurane is negligible during procedures of less than 45 min.

Key Words: ANESTHETICS, VOLATILE—enflurane. INTERACTIONS, DRUG—atracurium, enflurane. NEUROMUSCULAR RELAXANTS, ATRACURIUM.

Inhalation anesthetics potentiate neuromuscular blockade produced by *d*-tubocurarine and pancuronium (1–5). In this respect, enflurane appears to be more potent than halothane and at least as potent as isoflurane (5). The potency of the newer neuromuscular blocking agents atracurium and vecuronium is also altered by enflurane, but the degree of potentiation seems to be less than that for pancuronium and *d*-tubocurarine (6,7). In one report, maximum atracurium blockade was not affected by the presence of enflurane (8).

The mechanism of action of the potentiating effect of inhalation anesthetics on neuromuscular relaxants is uncertain. A large portion of this interaction must take place at the neuromuscular junction because this phenomenon can be demonstrated in vitro (9,10). This implies that the full effect might not develop until the inhalation anesthetic has equilibrated with muscle tissue, which may take 1–2 h after stable end-tidal concentrations have been achieved (11,12). However, the in vitro studies (9,10) do not rule out a central component, the time-course of which could be more rapid.

The purpose of this study was to determine the time-course of the interaction between inhalation anesthetics and nondepolarizing neuromuscular blocking drugs. The infusion rate of a neuromuscular blocking drug was adjusted to maintain a predetermined degree of blockade, both before and after the introduction of the inhalation agent. This allowed each patient to serve as his or her own control. Plasma concentrations of the neuromuscular blocking drug were measured, and potentiation was defined as a decrease in plasma concentration corresponding to the same degree of blockade. Enflurane was chosen because of its profound potentiating effect on neuromuscular blockade. Atracurium was used as the neuromuscular blocking agent because its rapid

---

Received from the Departments of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal; and Faculté de Pharmacie, Université de Montréal, Montreal, Quebec, Canada. Accepted for publication November 21, 1990.

Address correspondence to Dr. Donati, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

elimination makes it flexible when administered as an infusion.

Methods

The protocol was approved by the Hospital Ethics Committee. After written informed consent had been obtained, 10 ASA physical status I or II adults, 18–75 yr old, scheduled for surgery of anticipated duration greater than 2.5 h, were studied. Patients with cardiac, pulmonary, hepatic, renal, or neuromuscular disease were excluded. Other exclusion criteria included abnormal serum electrolyte levels, hypovolemia, anemia, airway abnormality, a history of multiple allergies, and the concurrent administration of drugs interfering with neuromuscular function.

The patients were premedicated according to the choice of the anesthetist. In the operating room, electrocardiographic, pulse oximetry, and noninvasive blood pressure monitors were applied. Anesthesia was induced with 15–30 μg/kg alfentanil and 3–5 mg/kg thiopental. The patients' lungs were then ventilated, using a face mask, with 70% nitrous oxide in oxygen. Stimulating electrodes were placed over the ulnar nerve at the elbow. The arm and forearm were immobilized in a splint, and the force of contraction of the adductor pollicis muscle was recorded with a Grass FT-10 transducer. An intravenous cannula dedicated to blood sampling was inserted into the ipsilateral antecubital vein. Supramaximal train-of-four stimulation (2 Hz for 2 s) was delivered and repeated every 12 s. After a stable baseline was established (5–10 min), 0.4 mg/kg atracurium was given intravenously. Tracheal intubation was performed when 100% blockade was attained and mechanical ventilation was instituted. End-tidal carbon dioxide was monitored with a mass spectrometer (SARA), and ventilation was adjusted to keep it within the range of 30–35 mm Hg. Anesthesia was maintained with 70% nitrous oxide and intermittent doses of 10–20 μg/kg alfentanil as required. Core temperature was maintained above 35°C.

When the first twitch height (T1) had recovered to 10% of baseline, an atracurium infusion (0.05%; 50 mg in 100 mL 5% dextrose in water) was started in the arm opposite the one used for neuromuscular recordings. A volumetric pump was used to adjust the infusion rate to keep neuromuscular blockade constant (T1 = 10% of control, or 90% blockade). When blockade had been stable for 15 min, 1.6%–1.7% end-tidal enflurane was introduced. Neuromuscular blockade was maintained constant by adjusting the infusion rate accordingly.

Blood (3 mL for each sample) was drawn 15 min before and 0, 5, 10, 15, 30, 45, 60, 90, and 120 min after the introduction of enflurane. The samples were heparinized and their temperature was lowered quickly by keeping them in ice for 10–15 min. They were then centrifuged and the plasma was acidified with sulfuric acid and frozen for later analysis.

Atracurium concentrations were measured in plasma using a specific high-performance liquid chromatography assay (13). Plasma samples (250 μL) containing 250 ng verapamil (internal standard) were reacidified with 10 μL of 0.5 M sulfuric acid. The plasma proteins were precipitated with 0.6 mL acetonitrile. After centrifugation, an aliquot of 50 μL of the supernatant was injected for analysis. The chromatographic separations were carried out on a Hichrom Spherisorb C_8 column (100 × 4.6 mm inner diameter, 5 μm particle size; Reading, U.K.) with a linear gradient mobile phase (pH 5) at flow rates of 1.7 mL/min. The mobile phase changed from 100% of 0.03 M phosphate buffer-methanol-acetonitrile (57.5:5:37.5) to 100% of 0.03 M phosphate buffer-methanol-acetonitrile (47.5:15:37.5) in 8 min. The Shimadzu fluorescence detector (Kyoto, Japan) excitation and emission wavelengths were set at 240 ng and 320 nm, respectively. The method is sensitive (limit of detection 20 ng/mL), reproducible (mean coefficient of variation under 5%), and linear for plasma concentrations of atracurium and laudanosine in the range 30–3000 ng/mL.

At each sampling time, neuromuscular blockade, atracurium concentration, and infusion rate were recorded. For each variable, the mean of the values obtained 15 min before and at the time of enflurane administration were taken as controls. Then the values were expressed as a percentage of control. Unless otherwise stated, the results are presented as mean ± standard error of the mean (SEM). Statistical analysis was performed using analysis of variance for repeated measurements. A P value <0.05 was considered to indicate statistically significant differences.

Results

There were four women and six men in the study. Mean age was 47 ± 6 yr and mean weight was 77 ± 7 kg. After the first dose of atracurium (0.4 mg/kg), twitch height did not reach 0% in three patients. In the other seven, T1 reappeared after a mean of 27 min (range, 22–30). Enflurane was added 59 min (range, 47–67) after injection of the initial dose of atracurium. The atracurium infusion rate required to maintain 90% blockade was 0.51 ± 0.10 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ in the

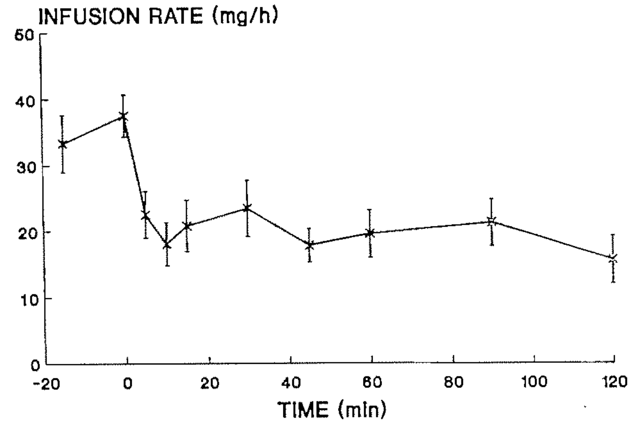


Figure 1. Infusion rate required to maintain blockade constant versus time. Enflurane introduced at time zero.

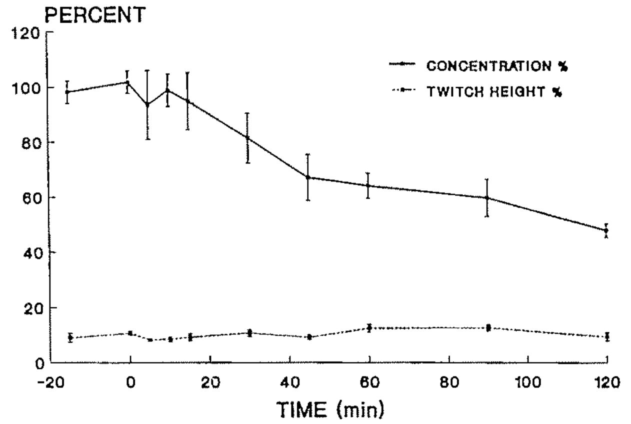


Figure 2. Atracurium plasma concentration required to maintain blockade constant. Enflurane introduced at time zero.

absence of enflurane. Because of the high concentrations of enflurane (3%–4%) and the high fresh gas flows given at the start of enflurane administration, a stable end-tidal concentration was achieved within 2–3 min. Immediately after the introduction of enflurane, twitch height decreased. To maintain the degree of neuromuscular blockade close to 90%, the rate of infusion of atracurium had to be decreased abruptly and was then maintained at 50%–60% of the control value for the remainder of the study period (Figure 1). In spite of the decrease in infusion rate, neuromuscular blockade was slightly more intense 5 min after the introduction of enflurane (92.7% ± 0.4%) than immediately before that event (89.3% ± 0.7%) ($P < 0.05$).

The plasma atracurium concentration at the start of enflurane administration was 730 ± 127 ng/mL. No significant decrease was observed during the first 30 min in spite of the changes in infusion rate made during this period. However, by 45 min the concentrations of atracurium corresponding to the same degree of blockade were only 67% ± 8% of control ($P < 0.01$), and 48% ± 2% after 2 h ($P < 0.01$) (Figure 2).

Discussion

This study shows that, with enflurane anesthesia given at a concentration of approximately 1 MAC (14), atracurium concentrations corresponding to 90% blockade may be reduced by one-half compared with nitrous oxide-narcotic anesthesia. However, this degree of potentiation is reached only after 2 h. For the first 30 min after the introduction of enflurane, no statistically significant potentiation (defined as a decrease in atracurium concentration for 90% blockade) was detected, and, if present, the intensity of this effect (19% in the present study) would be clinically insignificant. The degree of potentiation increased significantly between 45 and 120 min after administration of enflurane.

The methodology used in the present investigation differs from previous studies (1–4,6,7) in that we established no dose-response relationships. However, we were able to follow the interaction between enflurane and atracurium over time by measuring atracurium plasma concentrations corresponding to 90% blockade. The fact that each patient served as his or her own control allowed a reduction in the number of subjects required. The infusion rate decreased before plasma concentrations did because elimination of atracurium takes time, the terminal elimination half-life being approximately 20 min (15,16). Thus, the abrupt decrease in infusion rate in the first 5 min after the introduction of enflurane was associated with little change in plasma concentrations. It follows that the small increase in blockade observed at that time was associated with only a small degree of potentiation. There is also a time lag between a change in plasma concentration and change in effect, referred to in kinetic-dynamic studies as k_{eo} (17). For atracurium, this equilibration half-time is about 7 min (15), much more rapid than the time-course of the variations observed in the present study. Thus, concentrations of atracurium in plasma and at the neuromuscular junction were probably similar at all times.

Atracurium infusions have been used previously to maintain constant neuromuscular blockade in children (18). As in the present investigation, the atracurium requirements were found to decrease with time. Taking into consideration that a bolus dose was given before the infusion was started and that the inhalation anesthetic was administered from the beginning of this study, the results (18) suggest a significant decrease in atracurium requirements in the range 30–60 min after introduction of enflurane. Although plasma atracurium concentrations were not measured, the results are in agreement with those of the present study. With nitrous oxide-narcotic anesthesia, atracurium infusion rates to maintain 90% blockade remain constant for periods of at least 90 min in young as well as elderly adults (19). Thus, variations in infusion rate and plasma concentrations observed in the present study are much more probably due to enflurane, rather than to time alone.

Plasma concentrations of vecuronium have been measured during a controlled infusion of the drug (20). Patients were randomized to receive either a narcotic-nitrous oxide or enflurane-nitrous oxide anesthetic. After 2–3 h from the beginning of anesthesia, plasma vecuronium concentrations corresponding to 90% blockade were 165 ± 48 ng/mL without and 71 ± 34 ng/mL with enflurane, a 57% decrease. Although the time-course of potentiation was not investigated, the difference is compatible with the results obtained in the present study with atracurium. The time dependence of the interaction between *d*-tubocurarine and enflurane has been studied before (21). The plasma levels of the neuromuscular blocking drug were kept constant, and neuromuscular blockade was found to increase slowly with time.

The time-course of potentiation by enflurane is compatible with the time constant of enflurane for equilibrium in muscle tissue (11,12). The changes (a 3% decrease in twitch height without detectable alteration in plasma concentration) that were apparent by the fifth minute after enflurane was introduced could be the result of small quantities of enflurane reaching the neuromuscular junction. It has been suggested that the neuromuscular junction might be more richly supplied with blood than the rest of the muscle tissue. This was put forward as an explanation for the lack of change in *d*-tubocurarine potency after 40 min of halothane anesthesia (4). However, the results of the present study suggest a much slower equilibration with the neuromuscular junction because the potency of atracurium appeared to increase even after 2 h. In fact, the junctional area might have a richer blood flow than the rest of the muscle, but the adductor pollicis may be less well perfused than most other muscle groups. In other words, the "muscle group" might be heterogenous. For example, the diaphragm (22,23) and the masseter (24) are probably more richly supplied than the adductor pollicis. Therefore, enflurane potentiation might occur more rapidly in these muscles.

The results of the present investigation are in agreement with, and explain, apparently conflicting data from other studies. For example, it has been suggested that the newer relaxants, atracurium and vecuronium, are potentiated by enflurane and isoflurane to a lesser degree than are pancuronium and *d*-tubocurarine (6,7). However, the time delay between the introduction of the inhalation anesthetic and the injection of the neuromuscular blocking drug was longer in the studies involving pancuronium and *d*-tubocurarine (45 min) (1–3) than in the more recent investigations with atracurium and vecuronium (30 min) (6,7). Thus, the greater potentiation observed with pancuronium and *d*-tubocurarine might be a consequence of the longer exposure to enflurane or isoflurane. Similarly, maximum blockade produced by atracurium was unaltered with enflurane anesthesia (8) because the neuromuscular blocking agent was injected soon after the start of enflurane administration. However, in the same study the duration of action of atracurium increased in patients given enflurane, a finding consistent with a time-dependent potentiating effect. In a study during which both enflurane and neuromuscular blocking drugs were administered from the start of the anesthetic (25), enflurane did not affect onset time of blockade. Little, if any, prolongation of blockade was detected for vecuronium or atracurium, which recovered within 45 min of injection, but the duration of action of longer-acting pipecuronium and pancuronium (74–125 min) was affected markedly in the presence of enflurane. This, together with the increase in the duration of effect of additional doses of vecuronium and atracurium, strongly suggests a potentiating effect becoming clinically significant 45 min after starting administration of enflurane.

Clinically, the interaction between inhalation agents and neuromuscular blocking drugs is important. The dose of the latter may be altered by the presence of the former. However, this interaction is of negligible importance in the first 30–45 min after the introduction of enflurane, especially if the end-tidal concentration is less than that used in the present study (1.6%–1.7%). Because atracurium is indicated for procedures lasting 30–45 min, the presence of enflurane, even in concentrations as large as those used in this study, should not affect the dose required, or its duration of action. However, a decrease in requirement would be expected for longer procedures.

References

1. Fogdall RP, Miller RD. Neuromuscular effects of enflurane, alone and combined with *d*-tubocurarine, pancuronium, and succinylcholine, in man. Anesthesiology 1975;42:173–8.
2. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. The dependence of pancuronium and *d*-tubocurarine induced neuromuscular blockades on alveolar concentrations of halothane and Forane. Anesthesiology 1972;37:573–81.
3. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 1971;35:509–14.
4. Miller RD, Crique M, Eger EI II. Duration of halothane anesthesia and neuromuscular blockade with *d*-tubocurarine. Anesthesiology 1976;44:206–10.
5. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–49.
6. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. Anesthesiology 1984;60:102–5.
7. Rupp SM, McChristian JW, Miller RD. Neuromuscular effects of atracurium during halothane-nitrous oxide and enflurane-nitrous oxide anesthesia in humans. Anesthesiology 1985;63:16–9.
8. Keens SJ, Hunter JM, Snowdon SL, Utting JE. Potentiation of the neuromuscular blockade produced by alcuronium with halothane, enflurane and isoflurane. Br J Anaesth 1987;59:1011–6.
9. Waud BE, Waud DR. Effects of volatile anesthetics on directly and indirectly stimulated skeletal muscle. Anesthesiology 1979;50:103–10.
10. Waud BE. Decrease in dose requirement of *d*-tubocurarine by volatile anesthetics. Anesthesiology 1979;51:298–302.
11. Eger EI II. Anesthetic uptake and action. Baltimore: Williams & Wilkins, 1974.
12. Eger EI II. Uptake and distribution of inhaled anesthetics. In: Miller RD, ed. Anesthesia. 2nd ed. New York: Churchill Livingstone, 1986:625–47.
13. Varin F, Ducharme J, Besner JG. Determination of atracurium and laudanosine in human plasma by high-performance liquid chromatography. J Chromatogr Bio 1990;529:319–27.
14. Gion H, Saidman LJ. The minimum alveolar concentration of enflurane in man. Anesthesiology 1971;35:361–4.
15. Marathe PH, Dwersteg JF, Pavlin EG, Haschke RH, Heimbach DM, Slattery JT. Effect of thermal injury on the pharmacokinetics and pharmacodynamics of atracurium in humans. Anesthesiology 1989;70:752–5.
16. Parker CJR, Hunter JM. Pharmacokinetics of atracurium and laudanosine in patients with hepatic cirrhosis. Br J Anaesth 1989;62:177–83.
17. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to *d*-tubocurarine. Clin Pharmacol Ther 1979;25:358–71.
18. Goudsouzian N, Martyn J, Rudd GD, Liu LMP, Lineberry CG. Continuous infusion of atracurium in children. Anesthesiology 1986;64:171–4.
19. D'Hollander AA, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. Anesthesiology 1983;59:237–40.
20. Cannon JE, Fahey MR, Castagnoli KP, et al. Continuous infusion of vecuronium: the effects of anesthetic agents. Anesthesiology 1987;67:503–6.
21. Stanski DR, Ham J, Miller RD, Sheiner LB. Time-dependent increase in sensitivity to *d*-tubocurarine during enflurane anesthesia in man. Anesthesiology 1980;52:483–7.
22. Chauvin M, Lebreault C, Duvaldestin P. The neuromuscular blocking effect of vecuronium on the human diaphragm. Anesth Analg 1987;66:117–22.
23. Pansard JL, Chauvin M, Lebreault C, Gauneau P, Duvaldestin P. Effect of an intubating dose of succinylcholine and atracurium on the diaphragm and the adductor pollicis in humans. Anesthesiology 1987;67:326–30.
24. Smith CF, Donati F, Bevan DR. Differential effects of pancuronium on masseter and adductor pollicis muscles in humans. Anesthesiology 1989;71:57–61.
25. Swen J, Rashkovsky OM, Ket JM, Koot HWJ, Hermans J, Agoston S. Interaction between nondepolarizing neuromuscular blocking agents and inhalational anesthetics. Anesth Analg 1989;69:752–5.

ANESTH ANALG
1991;72:474–81

Additive Depressant Effects of Amiodarone Given With Halothane in Isolated Hearts

Rosemary T. Rooney, MB, FFARCSI, David F. Stowe, MD, PhD, Jure Marijic, MD, John P. Kampine, MD, PhD, and Zeljko J. Bosnjak, PhD

ROONEY RT, STOWE DF, MARIJIC J, KAMPINE JP, BOSNJAK ZJ. Additive depressant effects of amiodarone given with halothane in isolated hearts. Anesth Analg 1991;72:474–81.

The antidysrhythmic drug amiodarone may be given during general anesthesia. We examined the single and combined direct cardiac effects of amiodarone and halothane in the isolated guinea pig heart. Guinea pig hearts were isolated and perfused retrogradely through the aorta with oxygenated Krebs–Ringer solution at 37°C at constant pressure (55 mm Hg). Variables measured in 61 hearts included spontaneous heart rate (HR), atrioventricular conduction time (AVCT), isovolumetric left ventricular pressure (LVP), and coronary flow (CF). Amiodarone was administered as a single bolus into the retrogradely perfused aortic root and halothane was vaporized into the perfusing solution. Mean control values of pooled data before treatment were as follows: HR, 228 ± 4 (SEM) beats/min; AVCT (during atrial pacing at 240 beats/min), 82 ± 2 ms; LVP, 97 ± 4 mm Hg; and CF, 6.1 ± 0.2 $mL \cdot min^{-1} \cdot g^{-1}$. Amiodarone, 100 μg and 200 μg, decreased HR by 8% ± 2% and 8% ± 2%, increased AVCT by 5 ± 2 and 15 ± 3 ms, decreased LVP by 22% ± 3% and 27% ± 3%, and increased CF by 20% ± 1% and 40% ± 2%, respectively; all these changes were sustained for 60 min and, except for HR, were dose dependent. Halothane, 0.5% and 1%, transiently and dose-dependently decreased HR by 6% ± 2% and 12% ± 2%, increased AVCT by 4 ± 2 and 8 ± 2 ms, decreased LVP by 15% ± 3% and 31% ± 3%, and increased CF by 2% ± 1% and 6% ± 2%. In combination, the transient negative cardiac effects of halothane were statistically additive to the prolonged negative cardiac effects of amiodarone so that with 200 μg amiodarone plus 1% halothane, HR decreased by 26% ± 2%, AVCT increased by 24 ± 3 ms, LVP decreased by 58% ± 3%, and CF increased by 26% ± 2%. Our results indicate that halothane augments the cardiac depressant effects of amiodarone given as a single injection. Because the cardiac effects of a single injection of amiodarone are long-lasting, its administration before or during exposure to halothane might result in cardiac depression that is not easily reversible.

Key Words: ANESTHETICS, VOLATILE—halothane. HEART, ARRHYTHMIAS—amiodarone.

Amiodarone is a benzofuran derivative initially developed and used in Europe for the management of angina (1). After this early application amiodarone was found to possess antidysrhythmic properties (2); this has resulted in its extensive oral use for the treatment of both supraventricular and ventricular dysrhythmias (3–5). Amiodarone is primarily classified as a class III (prolongs action potential duration) antidysrhythmic agent; it is chemically unrelated to any other available antidysrhythmic agent (6). A major disadvantage of amiodarone has been that it must be administered orally for as much as several weeks before the maximal effect is achieved (3). This has limited its use in patients in whom an immediate effect is required.

Amiodarone, which has been used to treat atrial fibrillation and atrial flutter in postoperative and intensive care settings (7,8), was recently made available as an intravenous solution for experimental clinical study. Adverse cardiac effects observed with amiodarone include depression of sinus nodal (SA) rate (9), atrioventricular (AV) conduction (10), and left ventricular function (11,12), as well as coronary

---

Supported by grants from the National Institutes of Health (HL 34708 and HL01901), the American Heart Association Wisconsin Affiliate (88-GA-06), and an Anesthesiology Research Training Grant (GM 08377).

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana.

Received from the Anesthesiology Research Laboratory and the Departments of Anesthesiology and Physiology, Medical College of Wisconsin, and Zablocki VA Medical Center, Milwaukee, Wisconsin. Accepted for publication November 21, 1990.

Address correspondence to Dr. Stowe, The Medical College of Wisconsin, MFRC, Room A1000, 8701 Watertown Plank Road, Milwaukee Regional Medical Center, Milwaukee, WI 53226.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

vasodilation (11,12), especially in patients with cardiac impairment (12,13). These cardiac depressant effects are nontransient but long-lasting. Halothane, a potent volatile anesthetic, is well known to depress SA nodal rate (14–16), AV conduction (17), and left ventricular function (17,18), and to cause coronary vasodilation (19); these effects are reversible. Patients with cardiac disease receiving oral amiodarone preoperatively and undergoing general anesthesia and cardiopulmonary bypass have been observed to require greater postbypass inotropic and vasodilator therapy than patients not receiving amiodarone (20). Bolus injection of a single dose of amiodarone during administration of a volatile anesthetic could cause prolonged cardiac depression. This in vitro study was designed to compare the direct, dose-related cardiac depressant effects of a single aortic root injection of two concentrations of amiodarone alone and during perfusion of two concentrations of halothane.

Methods

Sixty-one albino short-haired female guinea pigs (250–450 g) were injected intraperitoneally with 10 mg ketamine and 1000 U of heparin and were decapitated when unresponsive to noxious stimulation. These methods have been detailed previously (17,21). After thoracotomy, the inferior and superior vena cava were cut and the aorta was cannulated distal to the aortic valve. The heart was immediately perfused with cold perfusate retrogradely through the aorta and was then excised. The perfusate, a modified Krebs–Ringer solution, had the following composition (in mM): Na^+ 137, K^+ 5.9, Mg^{2+} 1.2, Ca^{2+} 2.0, Cl^- 134, HCO_3^- 15.5, $H_2PO_4^-$ 1.2, pyruvate 2, glucose 11.5, mannitol 16, and EDTA (ethylenediaminetetraacetic acid 99%) 0.05. The solution was filtered (20 μm Astrodisc, Gelman Sciences, Ann Arbor, Mich.) and equilibrated with a 97% O_2–3% CO_2 gas mixture. Aortic pH, Pco_2, and Po_2, measured with a blood-gas analyzer (Radiometer ABL-2, Medtron Chicago Inc., Des Plains, Ill.) at the beginning and end of each experiment in each heart, were 7.41 ± 0.01, 35 ± 1 mm Hg, and 540 ± 5 mm Hg, respectively; there were no significant differences in values obtained at different times. Hearts were perfused with nonrecirculating perfusate and were submerged in a bath of perfusate solution. Perfusate and bath temperature were maintained at 36.5 ± 0.3°C using a thermostatically controlled water circulating system (Haake E52, Haake Buchlar Inc., Saddle Brook, N.J.). The perfusion pressure was maintained at 55 mm Hg with a 75-cm-high fluid column maintained with an overflow pump. Aortic root perfusion (coronary inflow) pressure was measured with a pressure transducer.

Two pairs of bipolar electrodes (Teflon-coated silver, diameter 125 μm, Cooner Wire Company, Chatsworth, Calif.) were placed in the superior right atrium and left ventricular septum at each heart to monitor intracardiac electrograms from which spontaneous sinoatrial rate and conduction times were measured as reported previously (17,21). An additional pair of electrodes was placed in the right atrium to pace the heart at 240 beats/min. Sinus cycle length was measured and heart rate (HR) was calculated from the superior right atrial beat-to-beat interval. Atrial-septal (AV) conduction time was determined with each beat, both during sinus rhythm and during pacing, from the superior right atrial to the left ventricular septal beat-to-beat interval.

The electrode signals were amplified 100–1000-fold, filtered at frequencies below 1 Hz and above 10 kHz, and displayed continuously on a polygraph (Astromed MT 9500R, Astro-Med Inc., West Warwick, R.I.) and on an image storing oscilloscope (Tektronix 5A26,5113, Tektronix, Beaverton, Ore.). Electrograms, left ventricular pressure (LVP), perfusion pressure, and coronary flow were intermittently tape recorded (Vetter D1, Vetter Co., Reberburg, Pa.) at 38 cm/s for later playback. Electrogram intervals were measured automatically by digital timer systems that allowed instantaneous beat-to-beat interval and rate analyses.

Left ventricular pressure was measured with a transducer connected to a thin, saline-filled latex balloon (Hugo Sachs Electronic KG, Germany) inserted into the left ventricle through the mitral valve from an incision in the left atrium. Balloon volume was adjusted initially to maintain a diastolic pressure of 0 mm Hg.

Coronary flow was measured electromagnetically using a 1.5-mm inner-diameter extracorporeal flow probe (BL610, Biotronex Laboratories Inc., Kensington, Md.) placed into the aortic inflow line. Zero flow was periodically established by temporarily bypassing the flow probe. The flow probe was calibrated daily by timed collections into a volumetric cylinder over the range of measured flow. Calibration curves were best fitted by nonlinear regression analysis ($r^2 >$ 0.98).

Halothane was introduced by switching to perfusate equilibrated with 0.5 and 1.0 vol% halothane, delivered by vaporizer (Fluotec vaporizer). The vaporizer was checked for accuracy at the delivered gas flow rate of 3 L/min by mass spectrometry (Medical Gas Analyzer 1100A, Perkin-Elmer, Norwalk, Conn.). Perfusate was collected at an aortic inflow side port into sealed, air-free, 1-mL vials for measurement of anesthetic gas concentrations by gas chromatography as previously described (17,21). Measured mean perfusate concentrations (±SEM) corresponding to vaporizer settings for 0.5 and 1.0 vol% halothane were (in mM) 0.18 ± 0.01 and 0.34 ± 0.01, respectively. Amiodarone HCl (a gift from Wyeth Laboratories, Philadelphia, Pa.) stock contained, per milliliter, 50 mg amiodarone HCl, 20 mg benzyl alcohol, and 100 mg polysorbate 80 (Tween) in water. Stock was diluted 100-fold in Krebs–Ringer solution for bolus intraaortic injection of 100 μg (0.2 mL) or 200 μg (0.4 mL) (155 and 310 nmol, respectively) of amiodarone. Adenosine HCl (Sigma-Aldrich, Milwaukee, Wis.) (200 μM in 0.2 mL) was injected before and at the end of each experiment to establish peak coronary flow.

Protocol

Drug-free control measurements were recorded after a 30-min period of stabilization. No hearts included in the study had more than two single premature atrial or ventricular beats per minute. Hearts were divided into six experimental groups: (A) 100 μg amiodarone only ($n = 9$); (B) 200 μg amiodarone only ($n = 8$); (C) halothane only (0.5 and 1 vol%) ($n = 17$); (D) 100 μg amiodarone plus halothane ($n = 11$); (E) 200 μg amiodarone plus halothane ($n = 11$); and (F) amiodarone vehicle ($n = 5$). After initial control (time 0 min) recordings, four groups randomly received, as a single intraaortic bolus, 100 μg (groups A and D) or 200 μg amiodarone (groups B and E). Ten minutes later (time 10 min), two of these groups (groups D and E) were exposed for 10 min to halothane, either to 0.5% or 1.0% first and then to the other concentration. Group C was exposed in random order to 0.5% and 1.0% halothane only. This was followed by a second 15-min halothane-free control period (time, 35 min). Group F received after the initial control (time 0 min) a single 0.4-mL intraaortic bolus of amiodarone vehicle (diluted 100-fold in Krebs–Ringer solution to contain 400 μg polysorbate 80 [Tween] and 80 μg benzyl alcohol). After exposure to the second concentration of halothane, there was a final 15-min halothane-free period (time 60 min).

Statistical Analysis

Each heart served as its own control for treatment effects. All data are expressed as mean ± standard error of the mean (SEM). Data were evaluated by two-way analysis of variance (Statview, Abacus Concepts, Calabasas, Calif., and CLR, Clearlake Research, Houston, Tex., software programs; Macintosh SE30 computer, Apple Computer Inc., Cupertino, Calif.). If variance was significant, means were compared by Fischer's least significant difference test, and a probability of less than 5% was considered statistically significant. Linear regression analysis was used to test whether effects of halothane were additive or synergistic to the effects of amiodarone. The linear regression slopes for halothane alone (±95% confidence intervals and SEM), derived from the individual data of each study variable as a function of the initial halothane-free controls (at time 10 min) and the two levels of halothane (at times 20 and 45 min), were compared to the slopes obtained in the presence of each of the two doses of amiodarone at the same time markers. Slopes were compared for parallelism ($P < 0.05$) by analysis of variance and means comparison tests.

Results

Table 1 shows the initial control values of all variables examined for each group. There were no significant differences among the six groups for any of the variables during the control period. Other studies from our laboratory show that in the absence of treatment there is no significant change in any of the variables measured for at least 3 h (unpublished observations).

The individual and combined effects of amiodarone and halothane on HR, AV time, LVP, and coronary flow are shown in Figures 1–4. Figure 1 shows that halothane alone significantly decreased HR; the decrease was dose dependent ($P < 0.001$). Amiodarone, given in single aortic root injections of 100 or 200 μg, caused an abrupt decrease in HR that was significant at 10 min and remained so for the ensuing 50 min; this effect was not dose dependent ($P > 0.5$). Introduction of halothane after amiodarone injection resulted in an additive decrease in HR compared with either dose of amiodarone alone; as with halothane alone, this effect was dose dependent ($P < 0.001$). Linear regression slopes for HR (beats per min/% halothane ± SEM) were −28.3 ± 5.0 for halothane alone, −30.0 ± 5.6 for halothane plus 100 μg amiodarone, and −32.7 ± 8.6 for halothane plus 200 μg amiodarone; these slopes were not statistically different. There was no significant difference between the HR responses to halothane plus 100 μg amiodarone and halothane plus 200 μg amiodarone.

Table 1. Initial Control Values for Each of Six Groups Before Administration of Halothane and/or Amiodarone

	Amiodarone (100 μg)	Amiodarone (200 μg)	Halothane only	Amiodarone 100 μg + halothane	Amiodarone 200 μg + halothane	Vehicle
n	9	8	17	11	11	5
HR (beats/min)	222 ± 4	226 ± 5	229 ± 3	234 ± 6	230 ± 5	231 ± 6
AVCT (ms)	56 ± 1	58 ± 2	56 ± 2	54 ± 1	56 ± 1	57 ± 2
AVCT (ms) at 240 beats/min	81 ± 2	87 ± 5	81 ± 2	80 ± 3	82 ± 2	84 ± 4
LVP (mm Hg)	95 ± 3	95 ± 4	102 ± 4	92 ± 4	103 ± 5	98 ± 7
CF ($mL \cdot min^{-1} \cdot g^{-1}$)	6.1 ± 0.2	6.2 ± 0.2	6.1 ± 0.5	6.2 ± 0.3	6.3 ± 0.3	6.2 ± 0.5

n, number of hearts per group; HR, spontaneous heart rate; AVCT, atrioventricular conduction time during atrial pacing; LVP, left ventricular pressure; CF, coronary flow.

All values are mean ± SEM.

There was no significant difference among the six groups for any variable.

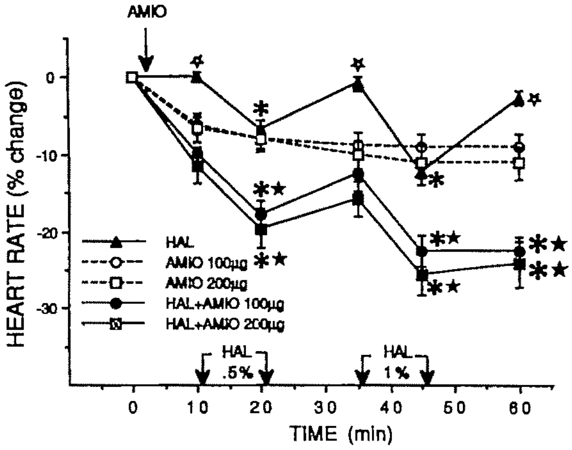


Figure 1. Effects of amiodarone and halothane on percentage change in spontaneous HR in five treatment groups. ☆ = treatments for each group at times 10, 20, 35, 45, 60 min that are *not* significantly different ($P > 0.05$) from their initial controls (at 0 min); all other treatment means are significantly different from their initial controls; ∗ = treatments for each group at times 20, 35, 45, 60 min that *are* different ($P < 0.05$) from the 10-min amiodarone alone (prehalothane) treatment; ★ = either dose of amiodarone plus either concentration of halothane that is different ($P < 0.05$) from the equivalent dose of amiodarone alone (vertical comparison at same time period). The effect of halothane, with and without amiodarone, was dose dependent; the effect of amiodarone alone was not dose dependent (statistics not shown). Total $n = 61$ hearts. Vehicle group data are not shown in the figures.

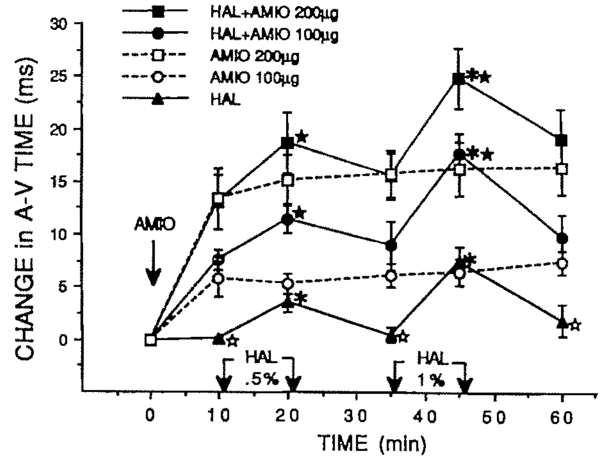


Figure 2. Effects of amiodarone and halothane on change in AV time in hearts paced at 240 beats/min. The effects of halothane, with and without amiodarone, and amiodarone alone were dose dependent (statistics not shown). See Figure 1 for explanation of symbols.

Figure 2 shows the changes in AV time during cardiac pacing at 240 beats/min. Halothane at 0.5% and 1.0% significantly increased AV time; this effect was dose dependent ($P < 0.01$). Bolus injection of amiodarone, 100 μg or 200 μg, also resulted in a significant increase in AV time that was sustained throughout the experiment; this effect of amiodarone was also dose dependent ($P < 0.001$). Introduction of halothane after amiodarone injection resulted in an additive increase in AV time that was significant compared with equivalent doses of amiodarone alone. Regression slopes for AV conduction time (ms/% halothane ± SEM) were 5.3 ± 1.7 for halothane alone, 6.2 ± 2.8 for halothane plus 100 μg amiodarone, and 4.9 ± 3.8 for halothane plus 200 μg amiodarone; these slopes were not statistically different. Non-drug control AV time and treatment AV time (amiodarone alone or with halothane) was significantly greater during pacing (Figure 2) than during sinus rhythm (data not shown), and exposure to each agent resulted in a more exaggerated increase in AV time during pacing than during sinus rhythm. Atrioventricular dissociation did not occur in any group.

Figure 3 shows that both halothane and amiodarone decreased systolic LVP significantly below control values. The effect of halothane was dose dependent ($P < 0.01$); the effect of amiodarone was not dose dependent. Administration of halothane after amiodarone injection caused a significant dose-dependent decrease in LVP. Regression slopes for

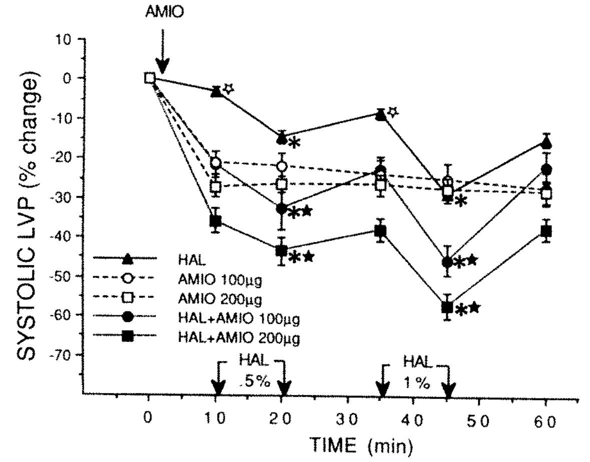


Figure 3. Effect of amiodarone and halothane on percentage change in systolic LVP. The effect of halothane, with and without amiodarone, was dose dependent; the effect of amiodarone alone was not dose dependent (statistics not shown). See Figure 1 for explanation of symbols.

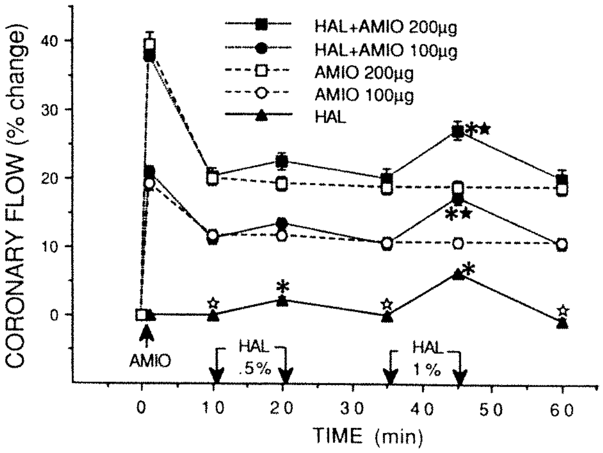


Figure 4. Effect of amiodarone and halothane on percentage change in coronary flow. This effect of halothane alone was not dose dependent; the effect of amiodarone alone or with halothane was dose dependant (statistics not shown). Adenosine increased flow 59% ± 1%. See Figure 1 for explanation of symbols.

LVP (mm Hg/% halothane ± SEM) were −34.3 ± 4.5 for halothane alone, −13.3 ± 6.3 for halothane plus 100 µg amiodarone, and −23.9 ± 5.9 for halothane plus 200 µg amiodarone; these slopes did not differ in a statistically significant way.

Figure 4 shows that halothane caused a small but significant increase in coronary flow; this increase in flow was not dose dependent. Injection of amiodarone produced a large increase in coronary flow that peaked at 1 min (increases of 20% with 100 µg and 39% with 200 µg); this effect was dose dependent. At 10 min coronary flow in these groups had decreased to approximately 50% of peak values, but flow was still significantly higher than initial control values and remained elevated throughout the experiments. Introduction of 1% halothane, but not of 0.5% halothane, with amiodarone resulted in an additive increase in coronary flow compared with amiodarone alone. Regression slopes for coronary flow ($\mathrm{mL \cdot g^{-1} \cdot min^{-1} \cdot \%\ halothane^{-1}}$ ± SEM) were 0.71 ± 0.64 for halothane alone, 1.01 ± 0.48 for halothane plus 100 µg amiodarone, and 1.75 ± 0.51 for halothane plus 200 µg amiodarone; these slopes did not differ in a statistically significant way. The greatest increase in coronary flow, induced by 200 µg of amiodarone, was significantly lower than the averaged (pre- and postcontrol) maximal increase in coronary flow obtained by bolus doses of adenosine (59% ± 1%).

In general, for all variables examined, halothane produced simple, additive (parallel) effects with amiodarone as determined by nonsignificant differences in halothane slopes with and without amiodarone as shown above. There was no evidence of synergistic effects. The effects of a single dose of amiodarone persisted during the period of study (60 min); the effects of halothane were transient. Bolus injection of the vehicle for amiodarone (group F) caused a relatively small (7% ± 2%) and transient decrease in LVP lasting about 5 min; there was no significant change from control between 5 and 60 min. The vehicle alone produced no changes in HR, AV time, or coronary flow (data not shown).

Discussion

A number of animal studies report the cardiac effects of amiodarone in vivo (11,22) and in vitro (23–25), but no studies have, to our knowledge, been performed to examine the direct cardiac effects of amiodarone with halothane. We chose the isolated retrogradely perfused guinea pig heart to investigate the direct and interactive actions of these agents. In this preparation, indirect cardiac effects resulting from changes in inflow capacitance and outflow impedance, as well as from hormonal and autonomic effects, can be avoided.

Results of this study demonstrate that (a) both amiodarone and halothane independently caused decreases in HR and systolic pressure and increases in AV time and coronary flow; (b) the changes in HR, systolic LVP, and AV time for halothane alone, and the changes in AV time and coronary flow for amiodarone alone were dose dependent; and (c) introduction of halothane, after amiodarone injection, caused significant additive increases in AV time and coronary flow and significant additive decreases in HR and systolic pressure. The evidence for additive (parallel), as opposed to synergistic, effects was provided by the statistically similar regression slopes for halothane alone and with each concentration of amiodarone. A limitation of this study is that we could not discern whether the doses of amiodarone used in this study reflect cardiac tissue or plasma levels that are clinically therapeutic.

Amiodarone has a wide range of electrophysiologic actions. It possesses both sodium (26) and calcium channel blocking properties (27). The calcium channel blocking activity could account for its vasodilatory and negative inotropic and chronotropic effects. Halothane, like amiodarone, has been demonstrated to depress calcium transients (28) and to slow inward calcium current in ventricular cells (29). These effects could, at least partially, also be responsible for halothane's depressant effect on the SA node (14–16) and on AV conduction time (17,21), as well as for its negative inotropic (17,18,21,28) and coronary vasodilatory (19) actions.

Sinus Rate Effects

An additive reduction of spontaneous HR with the combination of halothane and amiodarone was found in this in vitro study of direct cardiac effects. The observed negative chronotropic effects of amiodarone are similar to those noted in other in vitro studies, e.g., those in the isolated rabbit sinus node (23), the rabbit atrium (25), and the isolated dog heart (24). In vivo (22) and in vitro (23) studies demonstrate a reduction in the slope of diastolic depolarization and a decrease in the sinus node action potential duration, which may be due, at least in part, to the Ca^{2+} channel blocking effect of the drug. In humans and in experimental animals, the chronotropic effect of amiodarone has been variously described as positive (12) or negative (3,23,30) with a brief initial tachycardia followed by long-lasting bradycardia. The transient positive chronotropic responses that have been observed after intravenous administration most probably result from initial transient hypotension (31); this could trigger adaptive reflex responses that may be obscured by the direct negative chronotropic (23) action of amiodarone.

Our data confirm the findings of many other in vitro studies (14–17,21) that halothane has a direct dose-related negative chronotropic effect. The negative chronotropic effect is primarily a result of a reduction in the slopes of phase 4 and of phase 0 of the SA nodal cell action potential (15,16). The action potential effects of halothane can be reversed incompletely by increasing extracellular calcium and can be mimicked partially by verapamil, a calcium channel blocker. It does not appear to compete specifically with adrenergic receptor sites (16).

Atrioventricular Conduction Effects

Both amiodarone and halothane significantly prolonged AV conduction time, both in spontaneously beating and in paced hearts. Hearts were paced because the slowing of HR by these drugs would mask the well-known rate-dependent effects on AV conduction (10,14,15). During atrial pacing at 240 beats/min, exposure to both agents caused a more exaggerated prolongation of AV time than during sinus rhythm. Acutely administered amiodarone appears to exert its main conduction system effect at the AV node because amiodarone has been shown to prolong intranodal conduction time, with little or no effect on the atria, ventricles, or the His-Purkinje system (10,22). This is in agreement with the clinical impression that short-term intravenous amiodarone therapy is more effective for supraventricular dysrhythmias involving the AV node than it is for ventricular dysrhythmias (10).

Halothane has also been shown to prolong both AV conduction time (17,21) and intraventricular conduction time (21). The increase in AV nodal conduction delay may be due, at least partially, to nonspecific slowing of Ca^{2+} through its channels by both agents. Noncompetitive antagonism of adrenergic receptors by halothane (16,17) and amiodarone (32–34) could also underlie part of this effect. Whatever the mechanism, increased AV delay could account for the termination of paroxysmal supraventricular tachycardias (3,35) and for the lowering of the ventricular response in atrial flutter and fibrillation (36) induced by amiodarone.

Effects on Left Ventricular Pressure

Our data show that both amiodarone and halothane independently reduce isovolumetric LVP; the depression by halothane, but not by amiodarone, was dose dependent. The combination of amiodarone and halothane additively depressed LVP. Others have also reported that intravenous amiodarone has negative inotropic effects (13,32,37). One study attributed the cardiovascular depressant effect of intravenously administered amiodarone to the drug solvent Tween 80 (32). But oral amiodarone, in the absence of the solvent, is also reported to depress cardiac function

(30). Furthermore, we have demonstrated in this study that administration of the Tween-containing vehicle caused only a relatively small (7% ± 2%) transient fall in LVP that was long outlasted by the much larger fall in LVP induced by the injection of amiodarone dissolved in its vehicle. Therefore, the negative inotropic action observed in this study is attributable, almost completely, to immediate and continuing depression of contractility by amiodarone. The mechanism of the direct negative inotropic effect is not known. Recently, amiodarone has been reported to be a potent and retained competitor at dihydropyridine and phenylalkylamine (verapamil-like) calcium antagonist binding sites (33); however, other calcium-sensitive sites could be affected as well.

The depressant effects of halothane on the myocardium have been well studied (17–19) and appear to be partially due to an inhibition of the slow Ca^{2+} current across the sarcolemma (29) resulting in a decrease in myoplasmic calcium transients (28). In addition to the effect on transsarcolemmal Ca^{2+} flux, halothane may also restrict availability of Ca^{2+} to the contractile proteins and may reduce Ca^{2+} release from internal stores (18).

Effects on Coronary Flow

Our results show that both amiodarone and halothane produce coronary vasodilation in the isolated, perfused guinea pig heart. Because both agents depress HR and myocardial contractility, metabolic requirements are reduced and coronary flow should diminish. The increase in flow can therefore be assumed to be due to a direct vasodilatory effect of these agents at the coronary arterioles, which primarily regulate flow. Adenosine was capable of further dilating the coronary vasculature, however, indicting available coronary reserve. The submaximal coronary vasodilation induced by volatile anesthetics has been demonstrated previously in similar preparations (17,19). Amiodarone has also been shown to produce marked vasodilation when injected directly into the coronary arteries or when given as an intravenous bolus (12,31). The increased myocardial oxygen supply resulting from coronary vasodilation may account for the beneficial effects of continuous amiodarone infusion in the management of unstable and vasospastic angina (31,37). In addition, the bradycardia produced by amiodarone and halothane would be expected to result in an increase in coronary diastolic filling time and a decrease in myocardial oxygen consumption.

Clinical Correlation

Increasingly, patients receiving amiodarone for atrial or ventricular dysrhythmias are undergoing anesthesia for cardiac and noncardiac procedures (34,38–40). Recommended parenteral doses are 5–10-mg/kg intravenous bolus over 5–15 min; oral doses are 800–1600 mg/day. Amiodarone binds readily to tissues to exert its effects so that plasma levels measured after long-term oral administration (1–2.5 μg/mL) may not reflect a therapeutic effect. Because of its long half-life of 15–60 days (40), it is usually impractical to discontinue amiodarone therapy. There are several case reports (34,38,39) of anesthesia-related complications with amiodarone in which perioperative chronotropic and inotropic support was required. In a retrospective study (20) of 129 patients undergoing general anesthesia for endocardial resection and aneurysmectomy, a significantly greater number of the 33 patients receiving oral amiodarone preoperatively required postbypass and postoperative inotropic and vasodilator therapy compared with the 96 patients not receiving amiodarone (20). In another retrospective study (40), the incidence of complications during anesthesia for cardiac and noncardiac surgery in 16 patients on oral amiodarone (average serum level 1 μg/mL) and 30 control patients were compared; amiodarone-treated patients more often developed lower systemic vascular resistance, required intraaortic balloon pump augmentation, displayed a slower nodal rhythm or complete heart block, and exhibited atropine-resistant sinus bradycardia.

Although we can only extrapolate from our in vitro data to indicate relevance in the clinical situation, our results do help in understanding the direct cardiac effects of halothane in the presence of amiodarone. Our results show that amiodarone and halothane produce additive cardiac depressant effects and that the effects of amiodarone are not abolished by washout of the drug. It is likely that other volatile anesthetics would similarly accentuate the cardiac depressant effects of amiodarone. We suggest that, during procedures requiring general anesthesia, caution be exerted in the use of volatile anesthetics in those patients who have received intravenous or oral amiodarone. Moreover, it does not appear prudent to treat perioperative dysrhythmias with parenteral amiodarone because of the potential for prolonged depression of cardiac function.

References

1. Vastesaeger M, Gillot P, Rasson G. Etude clinique d'une nouvelle medication antiangoreuse. Acta Cardiol (Brux) 1967; 22:483–500.

2. Olsson SB, Brorson L, Varnauskas E. Class 3 antiarrhythmic agents in man. Observations from monophasic action potential recordings and amiodarone treatment. Br Heart J 1973;35: 1255–9.
3. Rosenbaum MB, Chiale PA, Halpern MS, et al. Clinical efficacy of amiodarone as an antiarrhythmic agent. Am J Cardiol 1976;38:934–44.
4. Waxman HL, Groh WC, Marchlinkski FE, et al. Amiodarone for control of sustained ventricular tachyarrhythmia: clinical and electrophysiologic effects in 51 patients. Am J Cardiol 1982;50:1066–74.
5. Haffajee CI, Love JC, Canada AT, Lesko LS, Asdourian G, Alpert JS. Clinical pharmacokinetics and efficacy of amiodarone for refractory tachyarrhythmias. Circulation 1983;67: 1347–55.
6. Vaughan EN, Williams DM. Classification of antidysrhythmic drugs. Pharmacol Ther 1975;1:115–38.
7. Installe E, Schoevaerdts JC, Gadisseux P, Charles S, Tremouroux J. Intravenous amiodarone in the treatment of various arrhythmias following cardiac operations. J Thorac Cardiovasc Surg 1981;81:302–8.
8. Faniel R, Schoenfield PL. Efficacy of i.v. amiodarone in converting rapid atrial fibrillation and flutter to sinus rhythm in intensive care patients. Eur Heart J 1983;4:180–5.
9. Touboul P, Atallah G, Gressard A, Kirkorian G. Effects of amiodarone on sinus node in man. Br Heart J 1979;42:573–8.
10. Morady F, DiCarlo LA Jr, Krol RB, Baerman JM, de Buitleir M. Acute and chronic effects of amiodarone on ventricular refractoriness, intraventricular conduction and ventricular tachycardia induction. J Am Coll Cardiol 1986;7:148–57.
11. De Boer LW, Nosta JJ, Kloner RA, Braunwald E. Studies of amiodarone during experimental myocardial infarction: beneficial effects on hemodynamics and infarct size. Circulation 1982;65:508–12.
12. Cote P, Bourassa MG, Delaye J, Janin A, Froment R, David P. Effects of amiodarone on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary artery disease. Circulation 1979;59:1165–72.
13. Bellotti G, Silva L, Filho A, et al. Hemodynamic effects of intravenous administration of amiodarone in congestive heart failure from chronic Chagas' disease. Am J Cardiol 1983;52: 1046–9.
14. Hauswirth O, Schaer H. Effects of halothane on sino-atrial node. J Pharmacol Exp Ther 1967;158:36–9.
15. Bosnjak ZJ, Kampine JP. Effects of halothane, enflurane and isoflurane on the SA node. Anesthesiology 1983;58:314–21.
16. Stowe DF, Dujic Z, Bosnjak ZJ, Kalbfleisch JH, Kampine JP. Volatile anesthetics attenuate sympathomimetic actions on the guinea pig SA node. Anesthesiology 1988;68:887–94.
17. Marijic J, Bosnjak ZJ, Stowe DF, Kampine JP. Effects and interaction of verapamil and volatile anesthetics on the isolated perfused guinea pig heart. Anesthesiology 1988;69:914–22.
18. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: a review of possible mechanisms. Anesthesiology 1987;67:745–66.
19. Hickey RF, Sybert PE, Verrier ED, Cason BA. Effects of halothane, enflurane and isoflurane on coronary blood flow autoregulation and coronary vascular reserve in the canine heart. Anesthesiology 1988;68:21–30.
20. Feinberg BI, LaMantia KR, Levy WJ. Amiodarone and general anesthesia—a retrospective analysis (abstract). Anesth Analg 1986;65:S49.
21. Stowe DF, Bosnjak ZJ, Marijic J, Kampine JP. Effects of halothane with and without histamine and/or epinephrine on automaticity, intracardiac conduction times, and development of dysrhythmias in the isolated guinea pig heart. Anesthesiology 1988;68:695–706.
22. Gloor HO, Urthaler F, James TN. Acute effects of amiodarone upon the canine sinus node and atrioventricular junctional region. J Clin Invest 1983;71:1457–66.
23. Goupil N, Lenfant J. The effects of amiodarone on the sinus node activity of the rabbit heart. Eur J Pharmacol 1976;39:23–31.
24. Kobayashi M, Godin D, Nadeau R. Acute effects of amiodarone in the isolated dog heart. Can J Physiol Pharmacol 1983;61:308–14.
25. Kadoya M, Konishi T, Tamamura T, Ikeguchi S, Hashimoto S, Kawai C. Electrophysiological effects of amiodarone on isolated rabbit heart muscles. J Cardiovasc Pharmacol 1985;7: 643–8.
26. Mason JW, Hondeghem LM, Kastzung BG. Block of inactivated sodium channels and of depolarization-induced automaticity in guinea pig papillary muscle by amiodarone. Circ Res 1984;55:278–85.
27. Follmer CH, Aomine M, Yeh JZ, Singer DH. Amiodarone-induced block of sodium current in isolated cardiac cells. J Pharmacol Exp Ther 1987;243:187–94.
28. Bosnjak ZJ, Kampine JP. Effects of halothane on transmembrane potentials, Ca^{++} transients and papillary muscle tension in the cat. Am J Physiol 1986;251:H374–81.
29. Bosnjak ZJ, Supan FD, Rusch NJ. The effects of halothane, enflurane, and isoflurane on calcium current in isolated canine ventricular cells. Anesthesiology 1991;74:340–5.
30. Heger JJ, Prystowsky EN, Jackman WM, et al. Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia or ventricular fibrillation. N Engl J Med 1981;305:539–45.
31. Remme WJ, Van Hoogenhuyze DC, Krauss XH, Hofman A, Kruyssen DA, Storm CJ. Acute hemodynamic and anti-ischemic effects on intravenous amiodarone. Am J Cardiol 1985;55:639–44.
32. Munoz A, Karila P, Gallay P, et al. A randomized hemodynamic comparison of intravenous amiodarone with and without Tween 80. Eur Heart J 1988;9:142–8.
33. Wagner JA, Weisman HF, Levine JH, Snowman AM, Synder SH. Differential effects of amiodarone and desethylamiodarone on calcium antagonist receptors. J Cardiovasc Pharmacol 1990; 15:501–7.
34. Koblin DD, Romanoff ME, Martin DE, et al. Anesthetic management of the parturient receiving amiodarone. Anesthesiology 1987;66:551–3.
35. Graboys TB, Podrid PJ, Lown B. Efficacy of amiodarone for refractory supraventricular tachyarrhythmias. Am Heart J 1983;106:870–6.
36. Strasberg B, Arditti A, Sclarovsky S, Lewin RF, Buimovici B, Agmon J. Efficacy of intravenous amiodarone in the management of paroxysmal or new atrial fibrillation with fast ventricular response. Int J Cardiol 1985;7:47–58.
37. Kosinski EJ, Albin JB, Young E, Lewis SM, LeLand OS Jr. Hemodynamic effects of intravenous amiodarone. J Am Coll Cardiol 1984;4:565–70.
38. Gallagher JD, Lieberman RW, Meranze J, Spielman SR, Ellison N. Amiodarone induced complications during coronary artery surgery. Anesthesiology 1981;55:186–8.
39. Navalgund AA, Alifimoff JK, Jakymec AJ, Bleyaert AL. Amiodarone induced sinus arrest successfully treated with ephedrine and isoproterenol. Anesth Analg 1986;65:414–6.
40. Liberman BA, Teasdale SJ. Anesthesia and amiodarone. Can Anaesth Soc J 1985;32:629–38.

Which Drug Prevents Tachycardia and Hypertension Associated With Tracheal Intubation: Lidocaine, Fentanyl, or Esmolol?

Steven M. Helfman, MD, Martin I. Gold, MD, Everard A. DeLisser, MD, and Claire A. Herrington, RN

HELFMAN SM, GOLD MI, DELISSER EA, HERRINGTON CA. Which drug prevents tachycardia and hypertension associated with tracheal intubation: lidocaine, fentanyl, or esmolol? Anesth Analg 1991;72:482–6.

Eighty patients, ASA physical status II–IV, scheduled for noncardiac surgery, were randomly assigned in a double-blind, placebo-controlled manner to receive a preintubation dose of either placebo, 200 mg lidocaine, 200 μg fentanyl, or 150 mg esmolol. Induction of anesthesia was accomplished with 4–6 mg/kg thiopental IV followed immediately by the study drug; 1–1.5 mg/kg succinylcholine was given at minute 1. Laryngoscopy and intubation were performed at minute 2 with anesthesia thereafter maintained with 1 MAC (±10%) isoflurane in 60% nitrous oxide in oxygen at a 5 L/min flow for 10 min. Heart rate was recorded every 15 s and blood pressure every minute from induction until 10 min after intubation. Maximum percent increases in heart rate (mean ± SE) during and after intubation were similar in the placebo (44% ± 6%), lidocaine (51% ± 10%), and fentanyl (37% ± 5%) groups, but lower in the esmolol (18% ± 5%) group ($P < 0.05$). Maximum systolic blood pressure percent increases were lower in the lidocaine (20% ± 6%), fentanyl (12% ± 3%), and esmolol (19% ± 4%) groups than in the placebo (36% ± 5%) group ($P < 0.05$), but not different from each other ($P > 0.05$). Only esmolol provided consistent and reliable protection against increases in both heart rate and systolic blood pressure accompanying laryngoscopy and intubation.

Key Words: INTUBATION, TRACHEAL—prevention of vascular responses. ANESTHETICS, LOCAL—lidocaine. ANALGESICS, FENTANYL. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol.

Hypertension and tachycardia usually accompany laryngoscopy and tracheal intubation (1). This response is undesirable, especially in patients with cardiovascular or intracranial disease. Topical and intravenous lidocaine, opioids, inhaled anesthetics, or adrenergic blockers are used in an attempt to blunt these potentially adverse hemodynamic responses. Lidocaine has been found to be inconsistently effective (2–6). Low doses of narcotics are effective, but may cause respiratory depression or rigidity, or they may prolong recovery time (2,7,8). Inhalation anesthesia is used but requires deep levels, may delay recovery after short operations, and can cause cardiovascular depression (9). Adrenergic blockers are effective, but longer acting agents outlast the transient intubation response and may cause hypotension or bradycardia; esmolol, an ultrashort-acting "cardioselective" β-blocker may not have these shortcomings (10–14). This double-blind, placebo-controlled study was designed to compare the effectiveness of postinduction, single-bolus placebo, lidocaine, fentanyl, and esmolol in blunting the hemodynamic intubation response.

Methods and Materials

Patients were eligible for the study if they were older than 21 yr, ASA physical status II, III, or IV, and scheduled for noncardiac surgery. Patients with atrioventricular conduction block greater than first-degree, congestive heart failure, cardiac arrhythmias, asthma, or use of β-blockers within the 24 h preceding surgery were excluded. The study was approved by the institutional Human Studies Subcommittee. Eighty patients gave written informed consent and

---

Supported in part by the VA Medical Center, in part by the University of Miami School of Medicine, Department of Anesthesiology, and in part by Dupont Pharmaceuticals.

Received from the Anesthesiology Service, VA Medical Center, Miami, Florida, and the Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida. Accepted for publication July 24, 1990.

Address correspondence to Dr. Gold, Anesthesiology Service (139), VA Medical Center, 1201 N.W. 16th Street, Miami, FL 33125.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

were randomly assigned (computer-designed) (20 in each group) to receive a preintubation dose of either placebo, 200 mg lidocaine, 200 μg fentanyl, or 150 mg esmolol. Ninety-nine patients were recruited but cancellations, schedule changes, or prolonged intubations required subtractions. This did not interfere with the 80 remaining consecutive patients that were properly randomized.

Preanesthetic medication consisted of 0.2 mg glycopyrrolate and 2–5 mg midazolam (according to size) IM 30–60 min before anesthetic induction with no significant changes in heart rate (HR) in any of the four groups. In the operating suite, standard monitors (electrocardiogram, Accutor noninvasive blood pressure monitor, pulse oximeter, SARA) were applied, and HR and systolic blood pressure (SBP) were recorded for 3 min. Denitrogenation and induction, at minute 0, was accomplished respectively by breathing oxygen and administering 4–6 mg/kg thiopental IV over a 15-s period; this was followed immediately by the study drug. Succinylcholine (1–1.5 mg/kg) was given at minute 1. Laryngoscopy and intubation (average duration less than 15 s) were performed by one investigator (S.M.H.) at minute 2. Data from patients in whom intubation required more than 30 s were excluded; the eight patients excluded for this reason were distributed equally in the four study groups. After confirmation of endotracheal tube position, anesthesia was maintained using 1 MAC (±10%) isoflurane in 60% nitrous oxide in oxygen at a 5 L/min flow for 10 min. Heart rate was recorded every 15 s and SBP every minute from induction until 10 min after intubation. Vecuronium (4–6 mg/70 kg) was the only additional drug given during this 10-min period. Study drugs consisted of a placebo (5% dextrose in water), 200 mg of lidocaine (prepared from 5 mL of 40 mg/mL strength), 200 μg fentanyl, or 150 mg esmolol. A fixed dose was used that had been prepared by a physician (E.A.D.) not involved in observation or data collection and the same volume (15 mL) was used for all four drugs in order to blind the other three investigators. Five-percent dextrose in water was added as necessary to achieve a final volume of 15 mL with all four drug solutions.

The data were analyzed using analysis of variance and the Newman–Keuls multiple range test to compare each of the four groups with each of the others at each time period or event, including the time of maximum increase in HR and SBP. Results were considered statistically significant if $P < 0.05$. Blood pressure data at minutes 2 and 3, the most likely time for hypertension to develop, were used for calculation of statistical power of percent change in SBP between (a) esmolol and placebo, (b) esmolol and lidocaine, and (c) esmolol and fentanyl.

Results

Some patients in the four groups (a) had preoperative hypertension, (b) were taking β-blockers, or (c) were taking diuretics. In the placebo group, the number of patients respectively was 2, 3, and 2; in the lidocaine group, 3, 2, and 2; in the fentanyl group, 3, 3, and 3; and in the esmolol group, 2, 3, and 3. No significant differences in numbers of patients with hypertension and/or taking β-blockers or diuretics existed among the four groups. No significant differences existed between any groups with regard to doses of midazolam given. There were no significant differences between groups with respect to age (46–53 yr), height (172.5–175 cm), weight (78–82 kg), body surface area (1.9–2.0 m^2), or thiopental induction dose (338–429 mg). Most patients were classified as ASA II in all four groups. Preinduction (baseline) HR and SBP were not statistically different in the four groups.

Heart rate before and after intubation and percent change from baseline levels are shown in Table 1. Figure 1 displays the percent change from baseline and HR from minute 0 to minute 5. Increases in HR during and after intubation were similar in the placebo, lidocaine, and fentanyl groups, but were lower in the esmolol group ($P < 0.05$). Systolic blood pressure values before and after intubation and percent changes in SBP (Table 2) were lower in the lidocaine, fentanyl, and esmolol groups than in the placebo group ($P < 0.05$), but not different from each other ($P > 0.05$). Figure 2 shows the maximal increase in HR and SBP after intubation. Power analysis of percent change of SBP at minutes 2 and 3 demonstrated values below the 80% level required to exclude a type II error (false conclusion that there is no difference between groups). Adverse effects such as severe bradycardia (HR < 50), hypotension (SBP < 90 mm Hg), bronchospasm, seizures, or rigidity did not occur.

Discussion

Only esmolol (150 mg) provided consistent and reliable protection against increases in both HR and SBP accompanying laryngoscopy and intubation. Lidocaine (200 mg) and fentanyl (200 μg) failed to protect against increases in HR. All three agents were effective in protecting against increases in SBP with no detectable difference between them. We used a

Table 1. Heart Rate

Time	HR				Percent change in HR			
	Placebo (*n* = 20)	Lidocaine (*n* = 20)	Fentanyl (*n* = 20)	Esmolol (*n* = 20)	Placebo (*n* = 20)	Lidocaine (*n* = 20)	Fentanyl (*n* = 20)	Esmolol (*n* = 20)
Baseline/induction	73 ± 3	72 ± 4	75 ± 4	71 ± 3	0	0	0	0
0 (Study drug)	72 ± 3	73 ± 4	74 ± 4	70 ± 3	−2 ± 1	1 ± 2	−2 ± 2	−1 ± 2
1 (Succinylcholine)	90 ± 4	91 ± 3	91 ± 3	78 ± 2^{a,b,c}	25 ± 5	31 ± 5	24 ± 5	12 ± 4
2 (Intubation)	98 ± 4	100 ± 3	96 ± 4	78 ± 2^{a,b,c}	37 ± 6	45 ± 7	30 ± 5	13 ± 5^{a,b,c}
3	103 ± 4	103 ± 3	101 ± 3	81 ± 2^{a,b,c}	44 ± 6	51 ± 10	37 ± 5	18 ± 5^{a,b,c}
4	100 ± 4	100 ± 4	96 ± 3	81 ± 3^{a,b,c}	40 ± 5	46 ± 9	31 ± 5	17 ± 6^{a,b}
5	102 ± 4	100 ± 3	94 ± 3	80 ± 3^{a,b,c}	42 ± 6	46 ± 9	27 ± 4	15 ± 5^{a,b}
6	100 ± 4	99 ± 3	91 ± 3	80 ± 3^{a,b,c}	40 ± 6	44 ± 8	23 ± 4	16 ± 5^{b}
7	97 ± 4	97 ± 3	88 ± 3	81 ± 3^{a,b}	36 ± 6	41 ± 7^{c}	20 ± 4^{a,b}	17 ± 6^{a}
8	96 ± 4	95 ± 3^{c}	86 ± 3^{b}	81 ± 3^{a,b}	34 ± 6	38 ± 6^{c}	16 ± 4^{b}	17 ± 6^{a,b}
9	95 ± 4	93 ± 3^{c}	84 ± 3^{b}	81 ± 3^{a,b}	33 ± 5	35 ± 6	14 ± 5	17 ± 6
10	93 ± 3	89 ± 3	81 ± 3	83 ± 3^{a}	31 ± 5	29 ± 6	10 ± 5	19 ± 6
11	93 ± 4	87 ± 3	78 ± 3	81 ± 3^{a}	30 ± 5	25 ± 5	6 ± 5^{a}	17 ± 6
12	91 ± 4	86 ± 3	78 ± 3	82 ± 3	27 ± 5	24 ± 5	7 ± 5^{a}	18 ± 5

HR, heart rate.
Values are mean ± SE.
$^{a}P < 0.05$ versus placebo.
$^{b}P < 0.05$ versus lidocaine.
$^{c}P < 0.05$ versus fentanyl.

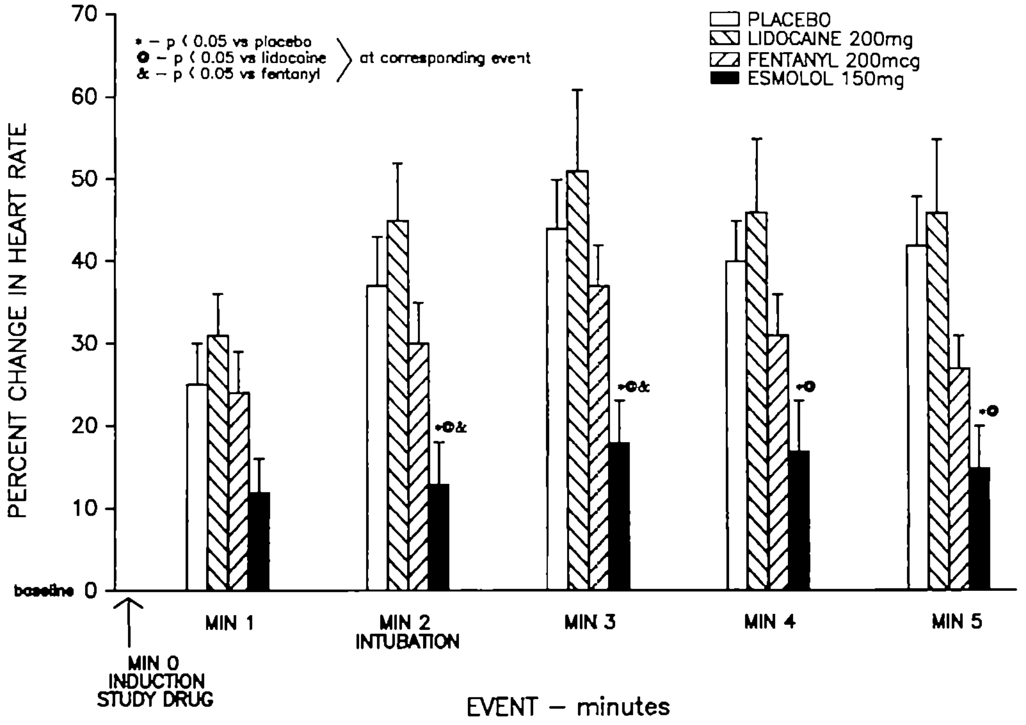


Figure 1. Percent changes in HR in the four groups from induction to minute 5. Esmolol is protective, but lidocaine and fentanyl are not. Values are mean ± SE.

fixed dose of each drug so that one investigator (E.A.D.) could rapidly, conveniently, and accurately prepare the solutions so that the same volume (15 mL) would always be used. In this manner the blinded investigators would not know which drug was being given. Also, one investigator (S.M.H.) intubated all 80 patients; in this way we believed the stimulus associated with intubation was, in all patients, as similar as possible under clinical conditions.

Lidocaine has been found to be only inconsistently effective in preventing cardiovascular changes associated with tracheal intubation. Doses of 1.5 mg/kg administered 4 min before intubation attenuated hy-

Table 2. Systolic Blood Pressure

	SBP				Percent change in SBP			
Time	Placebo ($n = 20$)	Lidocaine ($n = 20$)	Fentanyl ($n = 20$)	Esmolol ($n = 20$)	Placebo ($n = 20$)	Lidocaine ($n = 20$)	Fentanyl ($n = 20$)	Esmolol ($n = 20$)
Baseline/induction	132 ± 5	129 ± 4	134 ± 4	130 ± 4	0	0	0	0
0 (Study drug)	131 ± 4	127 ± 4	138 ± 5	134 ± 4	1 ± 3	−1 ± 2	3 ± 2	3 ± 2
1 (Succinylcholine)	136 ± 5	113 ± 5^a	122 ± 5^a	107 ± 4^a	4 ± 2	−11 ± 4^a	−8 ± 4^a	−17 ± 3^a
2 (Intubation)	160 ± 7	144 ± 8	139 ± 8	135 ± 4	23 ± 5	13 ± 6	4 ± 5^a	5 ± 4^a
3	176 ± 5	153 ± 8^a	150 ± 6^a	153 ± 5^a	36 ± 5	20 ± 6^a	12 ± 3^a	19 ± 4^a
4	172 ± 6	148 ± 7^a	143 ± 5^a	152 ± 5^a	32 ± 4	16 ± 6^a	8 ± 4^a	17 ± 3^a
5	168 ± 6	144 ± 5^a	135 ± 5^a	142 ± 5^a	28 ± 3	13 ± 4^a	2 ± 4^a	10 ± 3^a
6	155 ± 5	134 ± 5^a	126 ± 5^a	133 ± 5^a	19 ± 4	5 ± 5^a	−5 ± 3^a	3 ± 3^a
7	147 ± 5	127 ± 3^a	119 ± 5^a	125 ± 5^a	13 ± 3	0 ± 4^a	−10 ± 4^a	−4 ± 3^a
8	138 ± 5	121 ± 4^a	114 ± 4^a	119 ± 4^a	6 ± 3	−5 ± 4^a	−14 ± 3^a	−8 ± 3^a
9	134 ± 4	117 ± 4^a	109 ± 4^a	115 ± 4^a	3 ± 3	−8 ± 3^a	−17 ± 4^a	−11 ± 3^a
10	128 ± 5	110 ± 3^a	105 ± 3^a	114 ± 4^a	−2 ± 3	−13 ± 4^a	−20 ± 3^a	−11 ± 3^a
11	129 ± 5	109 ± 4^a	104 ± 3^a	113 ± 4^a	−1 ± 4	−14 ± 4^a	−21 ± 3^a	−12 ± 3^a
12	124 ± 5	109 ± 3^a	104 ± 3^a	113 ± 4	−5 ± 3	−14 ± 4	−21 ± 3^a	−12 ± 3

SBP, systolic blood pressure.
Values are mean ± SE.
$^a P < 0.05$ versus placebo.

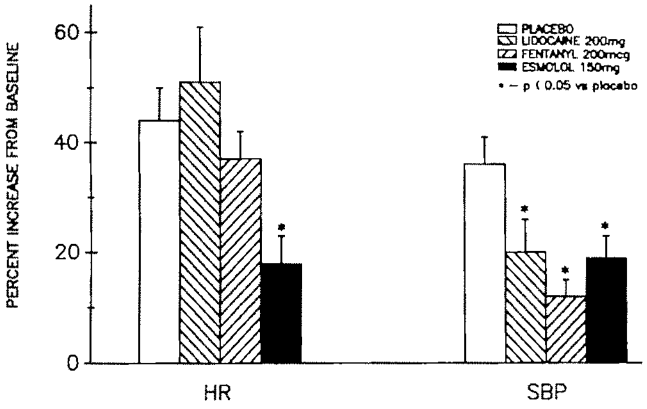


Figure 2. Maximum percent increases in HR and SBP after intubation. Only esmolol protects against increases in HR. All three drugs protect against increases in SBP.

pertension but not tachycardia (2). When given 2 min before intubation, lidocaine failed to protect against increases in SBP or HR (3), but when given 1.5 min before intubation, lidocaine did protect against changes in SBP (HR not studied) (4). Finally, 2 mg/kg lidocaine given 1 min before intubation was ineffective in the prevention of increases of HR or blood pressure (SBP) (5,6). We used a large dose of 200 mg of lidocaine (2.5 mg/kg in the average patient) 2 min before intubation. It still failed to protect against HR increases; SBP increases were, however, lessened. We believe the "usual" lidocaine dose of 100 mg (half the dose used in this study) will not reliably blunt increases in both HR and BP.

In a study of fentanyl at increasing doses of 0, 2, 5, 10, and 15 μg/kg given with a "sleep" dose of thiopental and pancuronium less than 4 min before intubation, it was found that, starting with the 3-μg/kg dose, increases in mean arterial pressure above preinduction values were prevented, but that 10 μg/kg was required to prevent increases in HR above baseline levels (7). Doses >5 μg/kg were associated with an 11%–45% incidence of hypotension (mean arterial pressure, 70 mm Hg or less). Others have found that both 1.5 and 3 μg/kg of fentanyl 4 min before intubation effectively attenuated both BP and HR increases (2,8). Starting at minute 5 the trend in our study was in the direction of lower SBP levels in the fentanyl group than in the lidocaine and esmolol groups. This may have been due to the synergistic effect of fentanyl with isoflurane. In our study, 2.5 μg/kg of fentanyl effectively blunted the BP but not the HR response to tracheal intubation.

Esmolol, with its 9-min elimination half-life, blunts tachycardia and hypertension when administered by bolus 2 min before intubation (11,12). It has been safely administered as a 300-mg bolus to healthy exercising subjects (13), and single-bolus injections of 100–200 mg 2.5–3 min before intubation have limited the HR and SBP responses (14). In this study, 150 mg esmolol was effective and safe in preventing the increases in HR and SBP after intubation. Mean HRs were in the narrow range of 78–83 beats/min during intubation and for the subsequent 10 min. After intubation the decrease in SBP was less with 150 mg of esmolol than with 200 μg of fentanyl ($P > 0.05$).

We failed to detect a difference in the ability of lidocaine, fentanyl, and esmolol to prevent SBP increases; this does not necessarily mean that no true difference in effect between the three drugs exists. However, power analysis of percent change of SBP at minutes 2 and 3, when one would expect the highest BP, results in values well below the 80% level required to exclude a type II error. It is probably safe to conclude that there is no difference between groups.

Weaknesses of our study are as follows: (a) a fixed dose of the study drug was given at a fixed time before intubation; if the drug had been given in greater dose or at a different time, lidocaine or fentanyl might have been more effective; (b) the small number of patients that existed in each group (20) might have precluded our ability to detect differences between groups; and (c) patients were premedicated with glycopyrrolate, which perhaps altered responses of HR to tracheal intubation. Although different dosages or time intervals may have influenced the effectiveness of fentanyl, they might also have caused hypotension or respiratory depression. With respect to lidocaine, the literature does not support predictable effectiveness even at 4 min before intubation. Despite the power analysis results, the small sample size may account for our inability to detect differences between lidocaine, fentanyl, and esmolol in preventing SBP increases. As far as use of glycopyrrolate in all patients in our study is concerned, in all four groups, we believe the administration of an anticholinergic before general anesthesia and tracheal intubation so increases safety that it would be inappropriate to omit it for the sake of increasing the pharmacologic priority of our study.

We conclude that 150 mg of esmolol provides consistent and reliable protection from increases in both HR and SBP during and after intubation. Lidocaine (200 mg) and fentanyl (200 μg) fail to protect against increases in HR, but do provide protection against increases in SBP equivalent to that provided by esmolol. We suggest that clinicians desiring to provide protection for their patients against intubation-related changes in HR and BP utilize an esmolol bolus 2 min before intubation as in this study.

References

1. Prys-Roberts C, Greene L, Miloche R, Foex P. Studies of anaesthesia in relation to hypertension. II. Haemodynamic consequences of induction and endotracheal intubation. Br J Anaesth 1984;43:531–47.
2. Splinter W, Cervenko F. Haemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients: effects of fentanyl, lidocaine and thiopentone. Can J Anaesth 1989;36:370–6.
3. Chraemmer-Jorgensen B, Hoilund-Carlsen P, Marving J, Christensen V. Lack of effect of intravenous lidocaine on hemodynamic responses to rapid sequence induction of general anesthesia. Anesth Analg 1986;65:1037–41.
4. Stoelting R. Circulatory changes during direct laryngoscopy and tracheal intubation. Anesthesiology 1977;47:381–3.
5. Laurito C, Baughman V, Becker G, Polek W, Riegler F, VadeBoncouer T. Effects of aerosolized and/or intravenous lidocaine on hemodynamic responses to laryngoscopy and intubation in outpatients. Anesth Analg 1988;67:389–92.
6. Hamill J, Bedford R, Weaver D, Colohan A. Lidocaine before endotracheal intubation: intravenous or laryngotracheal? Anesthesiology 1981;55:578–81.
7. Iyer V, Russell W. Induction using fentanyl to suppress the intubation response in the cardiac patient: what is the optimal dose? Anaesth Intens Care 1988;16:411–7.
8. Chung F, Evans D. Low-dose fentanyl: haemodynamic response during induction and intubation in geriatric patients. Can Anaesth Soc J 1985;32:622–8.
9. King B, Harris L, Greifenstein F, Elder J, Dripps R. Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 1951;12:556–66.
10. Coleman A, Jordan C. Cardiovascular responses to anaesthesia: influence of beta-adrenoreceptor blockade with metoprolol. Anaesthesia 1980;35:972–8.
11. Jacque J, Gold M, Grosnoff D, Whirley J, Herrington C. Does single bolus esmolol 2 minutes before intubation prevent tachycardia? Anesth Analg 1989;68:S133.
12. Jacque J, Gold M, Grosnoff D, Whirley J, Herrington C. Esmolol bolus before anesthetic induction for tachycardia-hypertension (abstract). Anesth Analg 1989;68:S134.
13. Ellenbogen K, McCarthy E, Pritchett E. Effects of bolus injection of esmolol in healthy, exercising subjects. Clin Pharmacol Ther 1987;41:455–9.
14. Parnass S, Rothenberg D, Kerchberger J, Ivankovich A. Single dose esmolol for prevention of hemodynamic changes of intubation in an ambulatory surgery unit. Anesthesiology 1989;71:A12.

ANESTH ANALG
1991;72:487–92

Computerized Continuous Infusion of Intravenous Anesthetic Drugs During Pediatric Cardiac Surgery

Frank H. Kern, MD, Ross M. Ungerleider, MD, James R. Jacobs, PhD, John L. Boyd III, MD, J. G. Reves, MD, David Goodman, BS, and William J. Greeley, MD

KERN FH, UNGERLEIDER RM, JACOBS JR, BOYD JL III, REVES JG, GOODMAN D, GREELEY WJ. Computerized continuous infusion of intravenous anesthetic drugs during pediatric cardiac surgery. Anesth Analg 1991;72: 487–92.

We evaluated the efficacy of a computer-assisted continuous infusion device (CACI) using a two-drug infusion of midazolam and sufentanil as an anesthetic technique during pediatric cardiac surgery. Seventeen pediatric patients were anesthetized with CACI using age-appropriate pharmacokinetic models for administering sufentanil and midazolam. Predicted CACI plasma concentrations were correlated with assayed plasma drug concentrations at eight predefined intervals. The accuracy was assessed using median absolute prediction error. We found that plasma levels predicted by CACI provided a reasonable approximation of measured plasma concentrations for both drugs. The median absolute prediction error for sufentanil during cardiopulmonary bypass was compared with measurements made off of cardiopulmonary bypass (both pre and post cardiopulmonary bypass) and were 49% and 32%, respectively, and for midazolam 44% and 32%, respectively. We conclude that (a) current kinetic models provide a reasonable estimate of plasma drug concentrations, and (b) the ease of administration and targeted plasma level provided by the CACI system is an alternative to inhalation anesthesia using calibrated vaporizers.

Key Words: ANESTHESIA, PEDIATRIC. ANESTHETIC TECHNIQUES, INTRAVENOUS INFUSIONS.

Continuous infusions of an opioid and of combinations of an opioid and a benzodiazepine have received substantial interest as anesthetic regimens for cardiac surgery (1). The advantage of these techniques is hemodynamic stability with a dosage scheme that results in a precise range of plasma concentrations that are both efficacious and pharmacologically sound, i.e., within a narrow therapeutic index (1–4). This approach provides a satisfactory anesthetic effect, with hemodynamic stability, minimal drug side effects, and a rapid recovery from anesthesia. Current techniques for continuous infusions of intravenous anesthetic agents rely on devices that administer drugs at a constant rate (e.g., Bard, Baxter) with volumetric infusion pumps. These systems allow for both drug administration in a controlled fashion and bolus supplementation where clinically necessary to suppress responses to intubation, skin incision, and sternotomy, for example. The advantages of these devices over traditional bolus techniques are less hemodynamic instability, suppression of cortisol and vasopressin responses during cardiopulmonary bypass, reduced need for vasoactive agents, and decreased total anesthetic dosages (1–4). The disadvantage is that these drugs are associated with such hemodynamic stability that without feedback to the anesthesiologist to assess actual plasma drug levels, relative anesthetic overdose is common. Recently, the concept of a computer-assisted continuous infusion system (CACI) that utilizes known pharmacokinetic data and a three-compartment model of drug redistribution to predict actual plasma drug levels in nanograms per milliliter has been proposed (5). The advantage of this system is that central compartment plasma levels can be attained, maintained, and regulated to anticipate noxious stimuli such as laryngoscopy and sternotomy (6). Thus, intravenous anesthetics can be adjusted in the same manner that alveolar concentrations of inhaled anesthetics are managed with a calibrated vaporizer.

Received from the Departments of Anesthesiology, Surgery, and Pediatrics, The Duke Heart Center, Duke University Medical Center, Durham, North Carolina. Accepted for publication November 13, 1990.

Address correspondence to Dr. Kern, Cardiac Anesthesia Service, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

The application of this technique to combined narcotic/benzodiazepine anesthetics for children undergoing cardiopulmonary bypass for congenital heart surgery is appealing in that constant anesthetic levels not only are important for hemodynamic stability but also play a role in balancing blood flow between systemic and pulmonary circulation (7) and in reducing pulmonary vascular responsiveness (8). The use of a combined opioid/benzodiazepine anesthetic reduces the high plasma concentrations of narcotic that are often necessary to provide adequate levels of anesthesia when used as a sole anesthetic, as reported for fentanyl, sufentanil, and alfentanil during adult cardiac and noncardiac surgery (1,2,3,5,9). This in turn may translate into less postoperative ventilatory depression and allow for early weaning from mechanical ventilatory support. For these reasons, we evaluated the efficacy and feasibility of a CACI device during pediatric cardiac anesthesia using a two-drug infusion system of midazolam and sufentanil.

Methods

System Description and Computer Model

The CACI system consists of a portable microcomputer (Datavue, model 25) interfaced to a digitally controllable drug infusion pump (Abbott Laboratories, Lifecare model 4) programmed with an age-appropriate pharmacokinetic model for midazolam and sufentanil. Sufentanil pharmacokinetics were defined using the three-compartment models derived from data for neonates, infants, and children reported by Greeley et al. (10); these models were scaled for age group and body weight. A separate pharmacokinetic model was used for four different age groups (1–30 days, 1 mo–2 yr, 2–12 yr, and 12–18 yr). Drug dosing was then adjusted for body weight within each age group. The pharmacokinetic model for midazolam was based on published adult pharmacokinetics scaled for body weight, i.e., there was no adjustment made for differing pharmacokinetics based on age (11). A schematic illustration of the CACI device is shown in Figure 1.

The CACI system included a burette filled with sufentanil and a burette filled with midazolam. The pump and intravenous tubing were primed with the infusate and attached to the proximal port of a central venous catheter or an indwelling peripheral venous catheter. The anesthesiologist used the computer keyboard to specify the patient's weight (kg) and the desired plasma concentration of sufentanil and midazolam (set point), which was entered in units of nanograms per milliliter. At 9-s intervals, a real-time simulation of a pharmacokinetic model for sufentanil and midazolam predicted the current plasma concentration. At these same intervals, the set point and the predicted concentration were acted on by the infusion algorithm to determine the optimal drug infusion rate required to achieve or maintain the set point by the end of the next 9-s interval. Every 9 s the computer interrogated the infusion pump to obtain information about the volume of drug infused and about the error status of the pump. The infusion rate used by the pump was communicated electronically to the host computer and entered into the pharmacokinetic simulation so that the next prediction could be computed. During a significant error condition such as occlusion of the intravenous catheter, the pump automatically reverted to an infusion rate of 0 mL/h, but because this information was transmitted to the host computer, which also alerted the user of the specific error condition, the infusion algorithm automatically compensated for the period of interruption when the problem was corrected. The software program allowed the anesthesiologist to adjust the set point as frequently as clinically indicated.

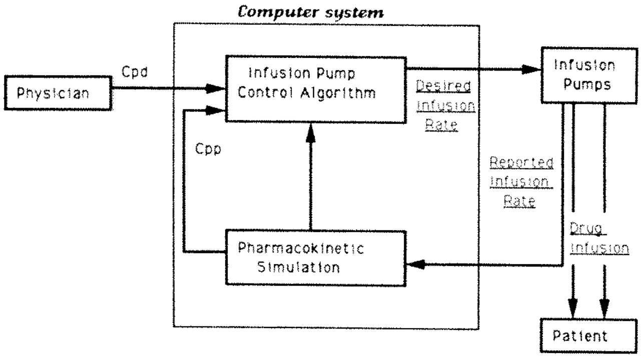


Figure 1. Schematic representation of the CACI system. Cpd = desired plasma drug concentration; Cpp = predicted plasma drug concentration using the computer-driven pharmacokinetic model.

The drug infusion algorithm has been described in detail by Jacobs (12).The pharmacokinetic simulation was implemented using difference equations forming a discrete approximation to the linear differential equations describing the three-compartment open pharmacokinetic model with drug administration into the central compartment and drug elimination from the central compartment (13).

Patients and Protocol

After Internal Review Board approval and informed parental consent, 17 pediatric patients ranging in age from 3 days to 16 yr undergoing general anesthesia and cardiopulmonary bypass (CPB) for repair of congenital cardiac defects were studied. Exclusion criteria for our study included history or biochemical evidence of hepatic or renal disease or use of enzyme-inducing drugs, e.g., phenobarbital. In two patients a pump malfunction resulted in early termination of the study, and these data points were not included in the results. Oral premedication consisting of 3 mg/kg meperidine, 0.1 mg/kg diazepam, and 2 mg/kg pentobarbital was administered to all children over 9 mo of age approximately 1 h before arrival in the operating room. Children under the age of 9 mo received no premedication.

Anesthetic induction was achieved using the CACI system in eight patients. These patients came to the operating room with central or peripheral intravenous catheters in place. In the remaining nine patients, anesthesia was induced using halothane by face mask. On achieving an adequate level of anesthetic, a peripheral intravenous catheter and intraarterial cannula were placed, halothane was discontinued, and the CACI delivery system was begun. All patients received pancuronium as the sole muscle relaxant. Initial loading doses of sufentanil and midazolam were targeted to achieve a plasma concentration ranging between 0.5 and 3 ng/mL and 25 and 100 ng/mL, respectively. Appropriate levels of anesthesia were determined by the anesthesiologist by assessing hemodynamic response to surgical stimuli and were adjusted by altering the predicted plasma level of midazolam and sufentanil with the CACI system. The end-point for the titration of the two drugs was stable hemodynamics, not specific plasma concentration, and therefore individual variability in pharmacokinetics and required plasma concentrations were approached in the same manner as with a calibrated vaporizer. The CPB circuit used polypropylene tubing and a Cobe membrane oxygenator, which have minimal absorption of sufentanil or midazolam (14).

At eight predetermined intervals, the predicted drug concentrations for midazolam and sufentanil were recorded and arterial blood samples were drawn for analysis of plasma sufentanil and midazolam levels. A 10-min period was allotted for drug equilibration after any increase in infusion rate to assure stable drug levels. The sampling intervals were (a) postinduction, (b) sternotomy, (c) pre-CPB, (d) CPB before cooling, (e) CPB with stable hypothermic temperature, (f) CPB rewarmed to normothermia, (g) after separation from CPB, and (h) sternal closure. A total of 240 samples were assayed, 120 for midazolam and 120 for sufentanil. Each sample was immediately placed on ice. Once all 16 samples were collected for each patient (eight midazolam and eight sufentanil), the samples were centrifuged and the plasma was transferred to new tubes for storage at −70°C until assayed. Plasma concentrations of sufentanil and midazolam were determined in duplicate by radioimmunoassay and high-performance liquid chromatography, respectively, for comparison with predicted CACI drug concentrations (15,16). At all eight sampling intervals, heart rate, mean arterial blood pressure, central venous pressure, and any patient response were recorded.

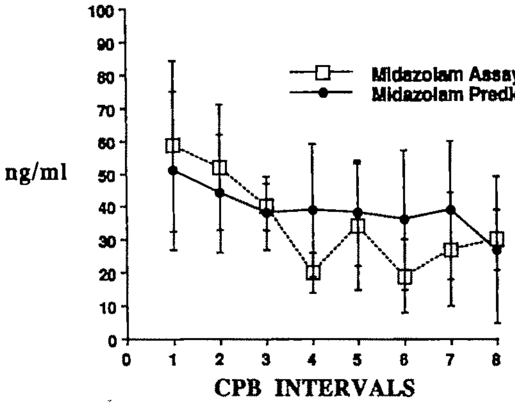


Figure 2. Graphic representation of the mean ± SD of the CACI-predicted concentrations and the actual measured plasma concentrations for midazolam. Predefined intervals are (1) postinduction, (2) sternotomy, (3) pre-CPB, (4) on CPB before cooling, (5) CPB with stable hypothermic temperature, (6) rewarmed to normothermia on CPB, (7) after separation from CPB, and (8) sternal closure.

Results were expressed as mean ± SD for both the predicted and assayed levels of both drugs. Accuracy of the CACI device was assessed by calculating the median of the percent absolute prediction error (%APE), where (%APE) = |M − P/P| × 100 and M = measured drug level, P = predicted drug level (17). The %APE is a measure of how well a predicted value performs when compared with a standard measurement method. Data are presented as a percentage of the values that typically "miss" the targeted measured value. The median rather than mean APE was chosen because we could not assume a normal distribution for the data.

Results

The mean ± SD plasma levels for midazolam and sufentanil are graphically represented in Figures 2 and 3. Both drugs show remarkably similar patterns for both the predicted and assayed drug concentrations. Concentrations predicted by CACI tended to underestimate the amount of drug in the central

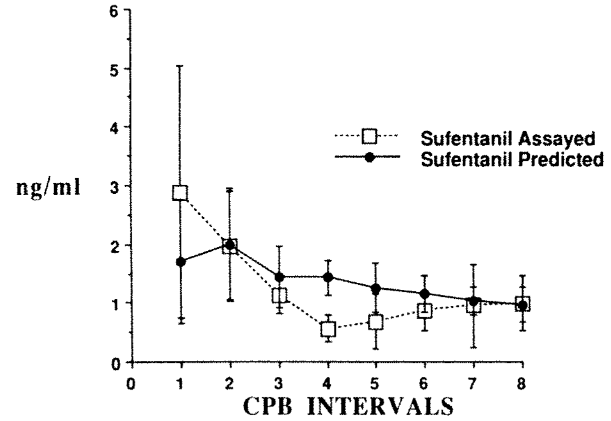


Figure 3. Graphic representation of the mean ± SD of the CACI-predicted concentrations and the actual measured concentrations for sufentanil. Predefined intervals are (1) postinduction, (2) sternotomy, (3) pre-CPB, (4) on CPB before cooling, (5) CPB with stable hypothermic temperature, (6) rewarmed to normothermia on CPB, (7) after separation from CPB, and (8) sternal closure.

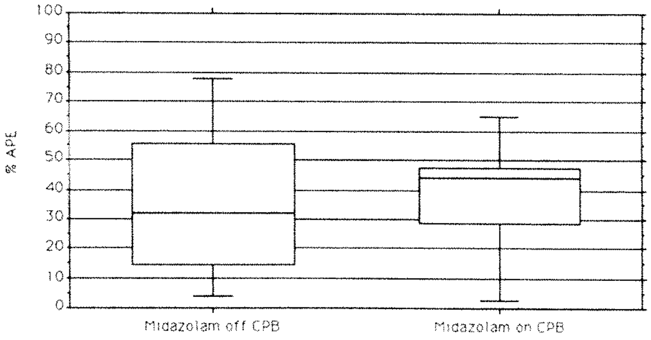


Figure 4. Plot of the median, twenty-five percent absolute prediction error and the full range of values for midazolam on and off CPB.

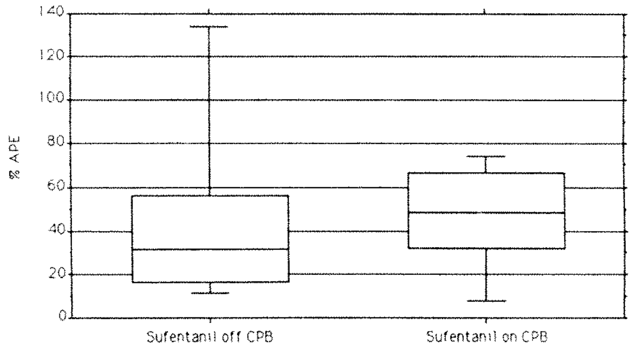


Figure 5. Plot of the median, twenty-five percent absolute prediction error and the full range of values for sufentanil on and off CPB.

compartment after administration of the loading dose (interval 1) when compared with the assayed level for both drugs. During the pre-CPB measurements (intervals 2 and 3), CACI provided a reliable estimate of the assayed plasma concentrations for both drugs. During CPB (intervals 4–6), the CACI-system-predicted levels overestimated the actual assayed level. After separation from CPB (intervals 7 and 8), predicted and measured levels were statistically similar. Median percent absolute prediction error (%APE) was measured for sufentanil and midazolam both during CPB and compared with measurements made off of CPB (both pre- and post-CPB values). The %APE for sufentanil on and off CPB was 49% and 32%, respectively. For midazolam the %APE on and off CPB was 44% and 32%, respectively. Thus the CACI device was more accurate, with a smaller percentage of values falling outside of the measured range when the patient was not on the extracorporeal circuit. The box plot of these data (Figures 4 and 5) shows the interquartile and full range for the data. These graphs show that the majority of CACI-predicted levels for sufentanil both on and off CPB fell within a narrow range. Midazolam levels predicted by CACI had a much greater degree of dispersion before and after CPB than during CPB. The total dose of sufentanil and midazolam administered during the operative period was 9.41 ± 2.38 and 113.8 ± 37.8 μg/kg, respectively. The average anesthetic time was 288 ± 97 min. Drug-related pertubations in hemodynamics were inconsequential during the loading period and maintenance phase of drug administration. Hemodynamic variables (blood pressure and heart rate) remained within 20% of baseline measurements. During separation from CPB, anesthetic levels were adequate as judged by hemodynamic stability and an absence of increased pulmonary vascular reactivity.

Discussion

Computer-assisted continuous infusions define a target plasma concentration based on a known pharmacokinetic model and produce drug levels that fall within a narrow therapeutic window known to be effective and to have minimal side effects (1). The advantage of these systems over conventional infusion devices that infuse drugs at a fixed rate lies in the exponentially declining infusion rate as well as the feedback provided by a predicted plasma concentration (1,2). This avoids the initial hemodynamic instability associated with bolus injections of drugs and with relative anesthetic overdose common to conventional narcotic-based infusion techniques. Several studies have evaluated the efficacy of opioids administered by a computer-assisted continuous technique during cardiac and noncardiac operations and have generally found greater hemodynamic stability, fewer side effects (hypotension, bradycardia, muscle rigidity, and postoperative ventilatory depression), and a reduction in the total dose of drug required to achieve satisfactory anesthetic conditions (1–3,9).

The application of CACI to anesthetizing children undergoing CPB for congenital heart surgery is appealing because anesthetic administration is important in maintaining hemodynamic stability as well as in balancing blood flow between the systemic and pulmonary circulation (6) and in reducing pulmonary vascular responsiveness (8). A critical period of anesthetic management for children and especially neonates is separation from CPB. Typically, management goals include administration of sufficient anesthetic drug to minimize oxygen consumption, reduce myocardial work and pulmonary vascular reactivity, yet at the same time avoid anesthetic-related hemodynamic suppression. Current strategies are to give patients bolus injections of moderately high doses of narcotic during the rewarming period of CPB to assure adequate levels of anesthesia. The negative aspects of this strategy are greater postoperative ventilatory depression and the inability to evaluate neuropsychiatric status in the immediate postoperative period.

In our study using CACI, we were able to maintain stable, effective levels of anesthesia during separation from CPB and still provide early postoperative neurologic assessment and early extubation when indicated. A combination of opioid and benzodiazepine was chosen to provide a balanced anesthetic technique (18). Each drug offered a specific pharmacologic benefit (sufentanil—analgesia, midazolam—sedation/amnesia) and, when used in combination, allowed for individual drug titration to attain the specific effect for each drug. The use of opioids alone may not be ideal, because relatively high plasma levels are required to achieve acceptable surgical conditions and because opioids do not provide the sedative and amnestic properties that complement a complete anesthetic (1,18). Therefore, we elected to evaluate the efficacy and feasibility of a two-drug CACI system using sufentanil and midazolam during pediatric cardiac anesthesia.

The initial sample measurement made after induction indicates that the kinetic model underestimated the assayed level. This suggests that the central compartment may be larger than predicted by this model. Several factors may contribute to the size of the central compartment: (a) patient age, (b) presence of capillary leak, and/or (c) preoperative pulmonary edema. Patient age is important because the volume of distribution has been shown to increase by as much as 21% within the first 3–4 wk of life and then decrease slowly during the next 12–24 mo (10,19). The current kinetic model uses an average value for neonatal (0–1 mo) volume of distribution for sufentanil and no kinetic change for midazolam and thus does not account for these early age-related changes in volume of distribution. Pulmonary edema, increased total body water due to shunt physiology, poor nutrition, or the use of prostaglandins E_1 may increase the patient's volume of distribution. These factors were not accounted for by the kinetic model.

The extracorporeal circuit adds several variables affecting drug biodisposition during CPB (20). The first is hemodilution. In adult patients, the extracorporeal circuit typically dilutes the extracellular fluid volume (ECF) by approximately 13%. In neonates and infants, the fluid volume added by the pump prime may dilute the extracellular fluid volume by as much as 60%. Additionally, pump oxygenators and pump tubing can bind drugs. This is especially a problem with the SciMed oxygenator, which uses a silicon rubber membrane (14). The binding of drug is less with polypropylene membranes such as the Cobe Variable Prime Membrane used in our institution (21). Our data demonstrate that initiation of bypass results in an overestimation of actual assayed plasma levels for both sufentanil and midazolam. This is reflected in Figures 2 and 3 and by the larger %APE (% predictive error) during the bypass period for both drugs when compared with pre- and post-CPB measurements. This most likely reflects hemodilution and possibly some binding of drug by the pump oxygenator.

The fact that assayed levels approach predicted level after CPB suggests that the current model may overestimate the rate of drug clearance or elimination half-life in pediatric patients undergoing CPB. Several investigators have shown both delayed clearance and prolonged elimination half-life for adult and pediatric patients after CPB (20,21). This most likely relates to the effects of nonpulsatile perfusion and hypothermia on hepatic and renal function as well as altered regional blood flow both during and after CPB (13,22,23). Changes in the kinetic model may be necessary to avoid plasma drug accumulation especially if CACI use is expanded to include postoperative sedation and pain control in an intensive care unit setting. In these circumstances, alterations in the kinetic model seem warranted.

This study demonstrates the feasibility and efficacy of a computer-assisted infusion device in neonates, infants, and children during pediatric surgery. Our data suggest that current kinetic models for sufentanil and midazolam provide a reasonable estimate of plasma drug concentrations in children and that neither the initiation of nor the separation from CPB limits the applicability of CACI techniques in this group of patients. The ease of administration and the feedback offered by estimated plasma concentrations provide a system that may be the equivalent of inhalation anesthesia using a calibrated vaporizer with the salutatory hemodynamic benefits of narcotic-based anesthetics. Because many pediatric cardiovascular patients are unable to tolerate the negative inotropic effect of inhalation anesthesia due to ventricular dysfunction, narcotic-based anesthetics are preferred. A CACI infusion of combined opioid/benzodiazepine offers a more rational and improved approach to bolus narcotic dosing. The greater stability in drug kinetics and reduced total drug requirement improve intraoperative hemodynamics, allow for early postoperative evaluation for neurologic sequelae, and provide for the potential of less postoperative ventilatory depression in the pediatric cardiac patient. Although discrepancies exist between predicted and assayed values, the ability of CACI to target intravenous anesthesia to a plasma level may provide an approach to the administration of intravenous anesthetics that is more physiologic and pharmacologic than current techniques. Minor refinements in the kinetic model would result in a better predictor of actual plasma concentrations and promote additional utility of this approach in postoperative and general intensive care unit management for neonates, infants, and children.

References

1. Glass PSA, Jacobs JR, Reves JG. Intravenous anesthetic delivery. In: Miller RD, ed. Anesthesia. 3rd ed. New York, Edinburgh, London, Melbourne: Churchill Livingstone, 1990:367–88.
2. Ausems ME, Vuyk J, Hug CC, Stanski DR. Comparison of a computer-assisted infusion versus intermittent bolus administration of alfentanil as a supplement to nitrous oxide for lower abdominal surgery. Anesthesiology 1988;68:851–61.
3. White PF. Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology 1983;59:294–300.
4. White PF, Coe V, Shafer A, Sung ML. Comparison of alfentanil with fentanil for outpatient anesthesia. Anesthesiology 1986; 64:99–106.
5. Alvis JM, Reves JG, Govier AV, et al. Computer-assisted continuous infusions of fentanyl during cardiac anesthesia: comparison with a manual method. Anesthesiology 1985;63: 41–9.
6. Glass PSA, Jacobs JR, Smith LR, et al. Pharmacokinetic model-driven infusion of fentanyl: assessment of accuracy. Anesthesiology (in press).
7. Hansen DD, Hickey PR. Anesthesia for hypoplastic left heart syndrome: use of high-dose fentanyl in 30 neonates. Anesth Analg 1986;65:127–32.
8. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA, Elixson EM. Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 1985;64:1137–42.
9. DeLange S, De Bruin NP. Alfentanil-oxygen anaesthesia plasma concentrations and clinical effects during variable-rate continuous infusions for coronary artery surgery. Br J Anaesth 1983;55:183S–9S.
10. Greeley WJ, deBruijn NP, Davis DP. Sufentanil pharmacokinetics in pediatric cardiovascular patients. Anesth Analg 1987; 65:1067–72.
11. Smith MT, Eadie MJ, Brophy T. The pharmacokinetics of midazolam in man. Eur J Clin Pharmacol 1981;19:271–8.
12. Jacobs JR. Algorithm for optimal linear model-based control with application to pharmacokinetic model-driven drug delivery. IEEE Trans Biomed Eng 1990;37:107–9.
13. Jacobs JR, Sheppard LC, Reves JG. Simulation of compartment models. Proceedings of the Eighth Annual Conference of the IEEE/EMBS 1986:702–4.
14. Rosen D, Rosen K, Davidson B, Broadman L. Fentanyl uptake by the Scimed membrane oxygenator. J Cardiothorac Anesth 1988;2:619–26.
15. Michiels M, Hendricks R, Heyants J. Radioimmunoassay of new opiate analgesics alfentanil and sufentanil: pharmacokinetic profile in man. J Pharm Pharmacol 1983;35:86–93.
16. Greenblatt DJ, Locniskar A, Ochs HR, Lauven PM. Automated gas chromatography for studies of midazolam pharmacokinetics. Anesthesiology 1981;55:176–9.
17. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 1981;9:503–12.
18. Hug CC. Does opioid anesthesia exist? Anesthesiology 1990; 73:1–4.
19. Greeley WJ, deBruijn NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg 1988;67:86–90.
20. Holley FO, Ponganis KV, Stanski DR. Effect of cardiopulmonary bypass on the pharmacokinetics of drugs. Clin Pharmacokinet 1982;7:234–51.
21. Koska AJ, Alexander R, Kramer WG. Effect of cardiopulmonary bypass on fentanyl distribution and elimination. Clin Pharmacol Ther 1980;29:100–5.
22. Mavroudis C. To pulse or not to pulse. Ann Thorac Surg 1978;25:259–71.
23. Larsen JA. The effect of cooling on liver function in cats. Acta Phys Scand 1971;81:197–207.

Sequestration of Glyceryl Trinitrate (Nitroglycerin) by Cardiopulmonary Bypass Oxygenators

Brian P. Booth, BSc, Mark Henderson, CSCP, Brian Milne, MD, Frank Cervenko, MD, Gerald S. Marks, DPhil, James F. Brien, PhD, and Kanji Nakatsu, PhD

BOOTH BP, HENDERSON M, MILNE B, CERVENKO F, MARKS GS, BRIEN JF, NAKATSU K. Sequestration of glyceryl trinitrate (nitroglycerin) by cardiopulmonary bypass oxygenators. Anesth Analg 1991;72:493–7.

The effectiveness of glyceryl trinitrate (nitroglycerin) in controlling myocardial ischemia and blood pressure during coronary artery bypass graft surgery is frequently lost during surgery, possibly as a result of drug sequestration by the cardiopulmonary bypass circuit. The objective of this study was to utilize a gas-liquid chromatographic assay to determine the extent of removal of glyceryl trinitrate from the priming fluid by the bubble and membrane oxygenators. The apparatus was maintained at either 25 or 37°C, the two extreme temperatures experienced by the patient during bypass surgery. At apparent steady state, the circulating glyceryl trinitrate concentration was decreased by 20.6%, 46.6%, and 67.3% with the Maxima membrane oxygenator, Cobe membrane oxygenator, and Bentley bubble oxygenator, respectively. The three-layer defoaming filters that are used in the Bentley bubble oxygenator were studied by immersing each of the three filters in fluid containing 60 nM glyceryl trinitrate and monitoring the drug concentration in Plasmalyte. The filters sequestered approximately 90% of the glyceryl trinitrate from the bathing solution of which 31% was recovered with a single methanol wash of the polyurethane filter. These data demonstrate that the different oxygenators used in the cardiopulmonary bypass circuit remove glyceryl trinitrate to varying degrees from the circulating fluid.

Key Words: PHARMACOLOGY, NITROGLYCERIN. ANESTHESIA, CARDIOVASCULAR—cardiopulmonary bypass.

One recent application of glyceryl trinitrate (GTN; nitroglycerin) has been the treatment of ischemia and the control of blood pressure during coronary artery bypass graft (CABG) surgery (1). Unfortunately, the effectiveness of GTN in controlling blood pressure is sometimes lost during cardiopulmonary bypass (CPB). This may be due to alterations of the pharmacokinetics and the pharmacodynamics of GTN that occur with the onset of CPB (2). In this regard, Dasta et al. demonstrated lower plasma concentrations of GTN (increased clearance) during bypass in patients undergoing CABG surgery (3). Contrary to these findings, we have observed increased plasma concentrations of GTN (decreased clearance) during the CPB procedure in CABG patients (4).

We hypothesized that the increased clearance of GTN found by Dasta et al. (3) might have been due, in part, to sequestration of GTN by the CPB equipment, which consisted of a Bentley Spiraflo BOS-10S bubble oxygenator. Several reports have indicated that certain types of plastics, most notably polyvinylchloride, adsorb GTN (5). Because the components of the CPB unit are constructed extensively of plastic and because the patient's blood comes into intimate contact with these foreign surfaces, GTN removal may occur. The objective of our study was to determine to what extent bubble and membrane oxygenators remove GTN from the fluid circulating within them. Using a simplified CPB model and a gas-liquid chromatographic assay, we determined that GTN was adsorbed by both types of oxygenator, but to a greater extent by the bubble oxygenators.

Supported by a grant from the Heart and Stroke Foundation of Ontario and a Heart and Stroke Foundation of Canada Research Traineeship grant (B.P.B.).

Received from the Departments of Pharmacology and Toxicology, Anaesthesiology, and Surgery, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada. Accepted for publication November 14, 1990.

Address correspondence to Dr. Nakatsu, Department of Pharmacology and Toxicology, Queen's University, Kingston, Ontario, Canada K7L 3N6.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Materials and Methods

Chemicals

Glyceryl trinitrate was obtained as a solution (Tridil, 5 mg/mL) in ethanol, propylene glycol, and water (1:1:1.33, vol/vol/vol) from Du Pont Pharmaceuticals, Scarborough, Ontario. Isoidide dinitrate was a gift from Dr. L. Douglas Hayward, University of British Columbia, and was used as an internal standard in all GTN assays. Plasmalyte, a balanced electrolyte solution (with the following constituents in mEq/L: Na^+, 140; K^+, 5; Mg^{2+}, 3; Cl^-, 98; acetate, 27; gluconate, 23) at pH 7.4, was obtained from Travenol Canada, Inc., Mississauga, Ontario. Surfacil (Pierce Chemical Co. Ltd., Rockford, Ill.) was used as a 10% (vol/vol) solution in toluene to silanize all glassware in order to prevent adsorption of GTN to the glass.

Apparatus

The experimental apparatus consisted of a roller pump (Travenol model 3500; Sarins Inc., Ann Arbor, Mich.) connected either to a bubble oxygenator or to a membrane oxygenator by a 1.83-m length of polyvinylchloride tubing (Bentley Bypass 70 tubing, 95.25-mm inner diameter). A new length of polyvinylchloride tubing was used in each experiment.

The bubble oxygenator studied was a Bentley Spiraflo BOS-10S bubble oxygenator (Bentley Laboratories, Inc., Irvine, Calif.). The two types of membrane oxygenator studied were the Maxima Hollow Fiber oxygenator (Medtronic Blood Systems, Inc., Anaheim, Calif.) and the Cobe CML Blood Oxygenators kindly donated by Walter Poprawa and Karen Linker of Cobe Canada, Ltd. (Scarborough, Ontario).

Two Heto circulating waterbaths were used to maintain the apparatus at either 25 or 37°C.

Time-Course of Glyceryl Trinitrate Concentration in Plasmalyte

The temperature protocol was designed to simulate the temperatures experienced by patients during CABG surgery. Initially the apparatus was maintained at 37°C. This was followed by a 15-min period at 25°C, and then the apparatus was rewarmed to 37°C for the final 15-min period. Significant differences in the GTN concentrations at the different temperatures were determined by comparing the mean GTN concentrations during the 25°C and final 37°C period by Student's *t*-test for paired data ($P < 0.05$).

The circulating fluid was 1000 mL of Plasmalyte that had been warmed to 37°C. Glyceryl trinitrate was added to the Plasmalyte to give a concentration of 6×10^{-8} M before priming the apparatus, and a 4.0-mL sample was taken to ascertain the initial concentration of GTN. After priming the apparatus, 4.0-mL samples were withdrawn with ice-cold glass syringes via a sampling port on the oxygenator, placed in silanized glass tubes, and frozen at −20°C until the time of analysis. Samples were taken during each 15-min temperature period (37, 25, then 37°C again) at 0, 1, 2, 5, 10, and 15 min. A sample was taken as the system was cooled (at 28°C), and another sample was obtained as the system was rewarmed (at 34°C) to the final 37°C period. Significant differences in the loss of GTN among the three types of oxygenators were determined by one-way repeated-measures analysis of variance of the percent loss of GTN during the 25°C and the final 37°C periods ($P < 0.05$).

Immersion of Oxygenator Filters in Glyceryl Trinitrate-Plasmalyte Solution

The Bentley bubble oxygenator and the Cobe membrane oxygenator have defoaming filters incorporated into their structures. To determine the extent of GTN removal by the defoaming filter, the filter from the Bentley bubble oxygenator, which consists of three layers (polypropylene, polyurethane, and polyester tricot) was studied. Glyceryl trinitrate was mixed with 1000 mL of warmed Plasmalyte (37°C) to give a final concentration of 6×10^{-8} M. The polyurethane filter was immersed in the solution, which was then continuously mixed with a magnetic stirrer. Samples of the GTN-containing Plasmalyte were taken after 5 and 20 min of immersion. The filter was transferred to a fresh 2-L glass beaker, washed with 300 mL of GTN-free Plasmalyte, and wrung out by hand. The filter then was transferred to another 2-L glass beaker and washed with 200 mL of methanol. A 4.0-mL sample of the methanol wash was taken, and duplicate 1.0-mL aliquots were obtained. Isoidide dinitrate, the internal standard, was added and these samples were evaporated to dryness. The residue was redissolved in 100 μL of benzene and frozen at −20°C until analysis the following day. The polypropylene and polyester tricot filters were immersed together in the GTN-Plasmalyte solution after removal of the polyurethane filter, and samples were obtained and prepared as described above. To determine significant differences in the GTN concentrations in the Plasmalyte during each treatment, a one-way repeated-measures analysis of variance was

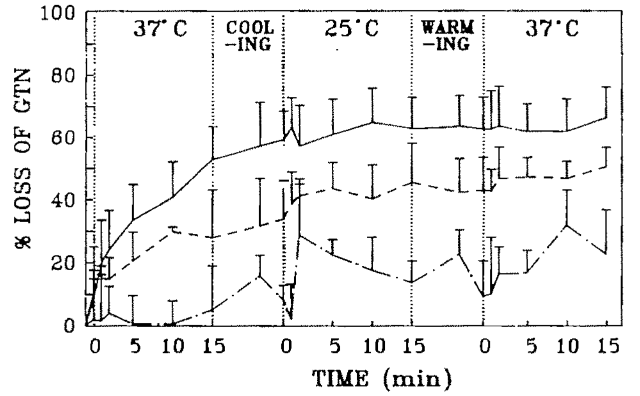


Figure 1. The mean (±SD) percent loss of GTN from the Plasmalyte during circulation through the Bentley bubble oxygenator (—) ($n = 4$), Cobe membrane oxygenator (---) ($n = 3$), and Maxima membrane oxygenator (—·—) ($n = 4$). The temperature protocol simulates the temperatures experienced by patients undergoing CABG surgery.

performed ($P > 0.05$). The amounts of GTN recovered from the filter washes were compared by Student's *t*-test for paired data ($P < 0.05$).

Gas-Liquid Chromatographic Assay for Glyceryl Trinitrate

The determination of GTN concentration was conducted using the method developed in this laboratory (6). The extraction of samples was the same as previously described (6) except that samples were extracted from Plasmalyte instead of plasma. Aqueous GTN standard curves were determined in duplicate for the concentration range of 10^{-9} to 6×10^{-8} M.

The same assay was used to determine the concentrations of the glyceryl dinitrates (6).

Results

Figure 1 shows the mean percent loss of GTN from the fluid circulating through the apparatus when equipped with each type of oxygenator. The mean GTN concentration for each time point was calculated from the data collected from the four oxygenators studied for each type of oxygenator. At apparent steady state, the mean GTN concentration in the circulating fluid was calculated from the means for each time point. The mean GTN concentration in the Plasmalyte was decreased by 67.3% with the Bentley bubble oxygenator, 46.6% with the Cobe membrane oxygenator, and 20.6% with the Maxima membrane oxygenator. These concentrations differed significantly from one another ($P < 0.05$). There was no measurable glyceryl dinitrate, a metabolite of GTN, at any time point during the course of the experiment.

Table 1. Mean Percent Glyceryl Trinitrate Remaining in Plasmalyte After Filter Immersion[a]

	Time (min)	% Initial GTN
	0	100
Polyurethane filter	5	26.2 ± 4.0[b]
	20	11.5 ± 2.7[b]
Polypropylene/polyester tricot	5	92.6 ± 0.5
	20	95.4 ± 1.2

GTN, glyceryl trinitrate.

Data are presented as mean ± SD ($n = 3$).

[a] Sixty nanomoles per liter GTN was added to 1000 mL of Plasmalyte and the two groups of filter layers were separately immersed in the fluid. The concentrations of GTN were determined by gas-liquid chromatographic assay and calculated as a percentage of the starting concentration.

[b] Significantly different from the three other groups ($P < 0.05$).

To determine if temperature affected GTN loss from the circulating fluid, the mean GTN concentrations during the 25°C and the final 37°C periods were compared for each type of oxygenator. The mean (±SD) GTN concentrations at 25 and 37°C were 4.9 ± 0.4 and 4.7 ± 0.2 ng/mL for the Bentley bubble oxygenator, 6.4 ± 0.3 and 5.7 ± 0.2 ng/mL for the Cobe membrane oxygenator, and 12.6 ± 1.4 and 12.3 ± 1.4 ng/mL for the Maxima membrane oxygenator, respectively. In each case, no significant differences were found, which indicated that temperature did not affect GTN loss.

The results of the filter immersion experiments are presented in Table 1. The concentration of GTN in the Plasmalyte before and after 5-min and 20-min periods of filter immersion are presented. After 5 min of polyurethane filter immersion, 26.2% ± 4.0% of the initial GTN concentration remained. After 20 min of immersion with this filter, only 11.5% ± 2.7% of the initial GTN concentration remained. The polypropylene and polyester tricot filters were immersed together in the GTN-Plasmalyte solution after removal of the polyurethane filter. After 20 min of immersion with these filters, 95.4% of the initial concentration of GTN remained in the Plasmalyte. The concentrations of GTN remaining after 5 and 20 min of immersion with the polyurethane filter did not differ significantly. However, both were significantly different from control and from both of the periods of immersion with the polyester tricot/polypropylene filters.

The percentages of GTN recovered by the methanol washes of the filters are presented in Table 2. After a single methanol wash of each filter, 31% of the initial amount of GTN in the Plasmalyte was recov-

Table 2. Mean Percent Glyceryl Trinitrate Recovered From Plasmalyte With Methanol[a]

	% GTN
Polyurethane filter	31.3 ± 22.2
Polypropylene/polyester tricot	5.6 ± 4.2[b]

GTN, glyceryl trinitrate.

Data are presented as mean ± SD ($n = 3$).

[a] After 20 min of filter immersion, each group of filter layers was removed from the Plasmalyte, rinsed with GTN-free Plasmalyte, wrung out by hand, and washed with 200 mL of methanol. Glyceryl trinitrate concentrations were determined by gas-liquid chromatographic assay, and GTN amounts were then calculated from the concentrations and the volumes of methanol or Plasmalyte used. The data were then presented as a percentage of the starting amount of GTN.

[b] Significantly different from the polyurethane filter ($P < 0.05$).

ered from the polyurethane filter, which was significantly different from the 5.6% recovered from the other two filter layers.

Discussion

The use of GTN to control blood pressure intraoperatively is frequently unsuccessful, and this failure may be attributed, at least in part, to the CPB procedure. There are four aspects of CPB—namely temperature, hemodilution, altered regional blood flow, and adsorption to plastic—that are believed to be factors contributing to alterations of the pharmacokinetics and the pharmacodynamics of GTN, as well as other drugs (2). Components of the CPB apparatus, with which the patient's blood comes in contact, are made of different types of plastic. The oxygenator, which temporarily performs gas exchange, is potentially the largest site for GTN sequestration. Extracorporeal oxygenation during CABG surgery can be achieved with either bubble or membrane oxygenators. These two types of oxygenator operate according to different principles (7). Bubble oxygenators mediate gas exchange by directly bubbling oxygen into the patient's blood (7,8). This design requires a chamber large enough to accomplish gas exchange and a filter to sieve bubbles from the blood that are produced as a result of oxygenation. In the membrane oxygenator, gas exchange occurs across a thin, microporous membrane (9). In both cases, the patient's blood comes into contact with foreign surfaces, which may serve as sites of adsorption for GTN.

As shown in Figure 1, there was GTN loss from the circulating Plasmalyte for all three types of oxygenator studied. The absence of detectable glyceryl dinitrate concentrations indicates that adsorption of GTN had occurred rather than degradation of the drug. When comparing the 25°C period to the final 37°C period, temperature did not appear to affect GTN loss once equilibrium had been attained.

The Bentley bubble oxygenator adsorbed the most GTN, and the Maxima membrane oxygenator removed the least. The Cobe membrane oxygenator adsorbed an intermediate amount of GTN. These differences appear to be due to the different plastics used in each type of oxygenator. Both types of oxygenator are constructed with polycarbonate outer shells, but the membrane oxygenators are made with polypropylene microporous membranes. Polypropylene reportedly does not adsorb GTN (5). The bubble oxygenator contains a three-layer filter, which consists of polypropylene, polyurethane, and polyester tricot (outside to inside), which sieves bubbles from the blood. Polyurethane is a material that has been reported to adsorb GTN (3,5). The results obtained with the Cobe membrane oxygenator, which is also made with polypropylene membranes, can be explained by the small defoaming filter situated in the reservoir atop the oxygenator. It is a smaller version of the polyurethane device used in the Bentley bubble oxygenator, and it removes GTN.

The data from Tables 1 and 2 support this explanation. In these experiments, the defoaming filters were removed from the Bentley bubble oxygenator; the different layers were separated; and each layer was immersed in GTN-containing Plasmalyte. The results in Table 1 show the percent of GTN remaining in the Plasmalyte at different times after the different layers of the filter were submerged. After 20 min of immersion with the polyurethane layer, only 11.5% of the GTN remained in the bathing solution, which indicated that 88.5% of the GTN was sequestered by this layer. The polypropylene and polyester tricot layers together removed 4.6% of the initial amount of GTN. Table 2 shows the percent of GTN that was recovered from the layers of the filter with a single wash of methanol. Thirty-one percent of the initial amount of GTN was recovered from the polyurethane layer, and 5.6% was recovered from the polypropylene and polyester tricot layers. These data confirm that the GTN was sequestered by the filter, especially the polyurethane layer. The results of these experiments indicate that the defoaming filter, particularly the polyurethane layer, is capable of removing substantial amounts of GTN.

It is important to point out that some of the GTN adsorbed by all three types of oxygenator occurred in the polyvinylchloride tubing that was used. Polyvinylchloride is known to adsorb GTN (5). However, because of its other qualities, polyvinylchloride is widely used in the CPB units. This use of polyvinylchloride tubing in the CPB circuit does not explain the differences in the plasma GTN concentrations observed by Dasta et al. (3) and Cervenko et al. (4). In the present study, we have accounted for this variable by using the same length of new polyvinylchloride tubing in each experiment. The differences in the amount of GTN lost in each type of oxygenator explain, at least in part, the differences in plasma GTN concentrations reported by Dasta et al. (3) and Cervenko et al. (4).

In summary, the data from these experiments demonstrate that the membrane oxygenator removed less GTN than the bubble oxygenator. This difference appears to be due to the materials used in the different oxygenators. The polypropylene in the membrane of the membrane oxygenator did not remove much GTN, whereas the polyurethane defoaming filter removed large quantities of GTN. Clinically, this may be important. The sequestration of GTN by the oxygenator during the CPB procedure would decrease the amount of GTN available to the patient and, as a consequence, would impair control of blood pressure.

We wish to thank Beth Inglis for her contributions, Winston Orford for his support and expertise, and Kristine Fleming of Baxter, Inc., for her help.

References

1. Flaherty JT. Nitrate tolerance: a review of the evidence. Drugs 1989;37:523.
2. Buylaert WA, Herrgods LL, Mortier EP, Bogaert MG. Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. Clin Pharmacokinet 1989;17:10.
3. Dasta JF, Weber RJ, Wu LS, et al. Influence of cardiopulmonary bypass on nitroglycerin clearance. J Clin Pharmacol 1986;26:165.
4. Cervenko FW, Milne B, Parlow J, Pym J, Nakatsu K, Elliot D. Effect of cardiopulmonary bypass with a membrane oxygenator on plasma nitroglycerin levels. Can J Anaesth 1989;36 (3 part II):S163.
5. Yacobi A, Amann AH, Baaske DM. Pharmaceutical considerations of nitroglycerin. Drug Intell Clin Pharm 1983;17:255.
6. Booth BP, Bennett BM, Brien JF, et al. Assay of glyceryl trinitrate, isosorbide dinitrate, and their metabolites in plasma by large-bore capillary column gas-liquid chromatography. Biopharm Drug Dispos 1990;11:663.
7. Ten Duis HJ, de Jong JFC, van Asseldonk AGM, Smit Sibinga CT, Wildevuur CRH. Improved hemocompatibility in open heart surgery. Trans Am Soc Artif Intern Organs 1978;24:656.
8. Liddicoat JE, Bekassy SM, Beall AC Jr, Glaeser AH, Debakey ME. Membrane vs. bubble oxygenator: clinical comparison. Ann Surg 1975;181:747.
9. Valdes F, Harasaki H, Meserko J, et al. Ex vivo evaluation of a new capillary membrane oxygenator. Trans Am Soc Artif Intern Organs 1981;27:270.

One Hundred Percent Incidence of Hemidiaphragmatic Paresis Associated With Interscalene Brachial Plexus Anesthesia as Diagnosed by Ultrasonography

William F. Urmey, MD, Karl H. Talts, MD, and Nigel E. Sharrock, MB, ChB

URMEY WF, TALTS KH, SHARROCK NE. One hundred percent incidence of hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia as diagnosed by ultrasonography. Anesth Analg 1991;72:498–503.

Interscalene brachial plexus anesthesia for shoulder surgery routinely includes sensory anesthesia of the fourth and fifth cervical nerves. The authors reasoned that some degree of diaphragm paralysis should result from interscalene blocks that produce surgical C3-C5 sensory anesthesia. In this investigation, ultrasonography was used to study the incidence of ipsilateral hemidiaphragmatic paresis during routine interscalene block, as it is a practical, sensitive, and low-risk method for diagnosing hemidiaphragmatic function without radiation exposure. Thirteen healthy patients received interscalene blocks using a paresthesia technique with 34–52 mL 1.5% mepivacaine with added epinephrine and bicarbonate. All developed cervical sensory anesthesia. Data were collected before and 2, 5, and 10 min after injection, and, when possible (11 of 13 patients), at hourly intervals after surgery. Changes from normal to paradoxical motion of the ipsilateral hemidiaphragm were seen in all 13 patients during sniff and Mueller maneuvers within 5 min (in 11 of 13 patients at 2 min). Diaphragmatic motion returned to normal in 10 of 11 patients between 3 and 4 h after injection and in the remaining patient by the fifth hour after injection. Diaphragmatic paresis appears to be an inevitable consequence of interscalene brachial plexus block when providing anesthesia sufficient for shoulder surgery.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interscalene block.

Winnie et al. showed that interscalene injection of local anesthetic can affect the cervical as well as brachial plexuses (1). Studies of the spread of local anesthetic associated with brachial plexus block using contrast labeling or sensory examination have shown that spread may extend to the cervical area with interscalene brachial plexus injections as small as 10 mL. The anatomic basis for rostral spread of local anesthetic is the continuous fibrous sheath that envelops both brachial and cervical plexuses (2,3). It is reasonable to assume, therefore, that rostral spread from interscalene local anesthetic injections could routinely interfere with ipsilateral hemidiaphragmatic function by blocking C-3 through C-5 motor nerves.

Although acute respiratory failure has been reported after brachial plexus block (4), the incidence of unilateral hemidiaphragmatic paresis during interscalene block has not previously been prospectively evaluated. When cases of diaphragmatic paresis have been documented, onset and duration have not been established.

The incidence of ipsilateral hemidiaphragmatic paresis varying from 28% to 80% has been found after *supraclavicular* brachial plexus block (5–7). The incidence during interscalene block may be greater because the injection is more cephalad and therefore closer to the cervical plexus. Also, in the above investigations diaphragmatic motion was evaluated by fluoroscopy, the conventional technique for diagnosing diaphragmatic paresis. The sensitivity of fluoroscopic diagnosis has been questioned (8,9) on the basis that it is dependent on qualitative observer interpretation of diaphragmatic motion during limited periods of time.

We sought to characterize more clearly the incidence, time of onset, and duration of ipsilateral hemidiaphragmatic paresis associated with interscalene brachial plexus anesthesia. Ultrasonography

---

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from the Department of Anesthesiology, The Hospital for Special Surgery, Cornell University Medical College, New York, New York. Accepted for publication November 14, 1990.

Address correspondence to Dr. Urmey, Department of Anesthesiology, The Hospital for Special Surgery, Cornell University Medical College, 535 East 70th Street, New York, NY 10021.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

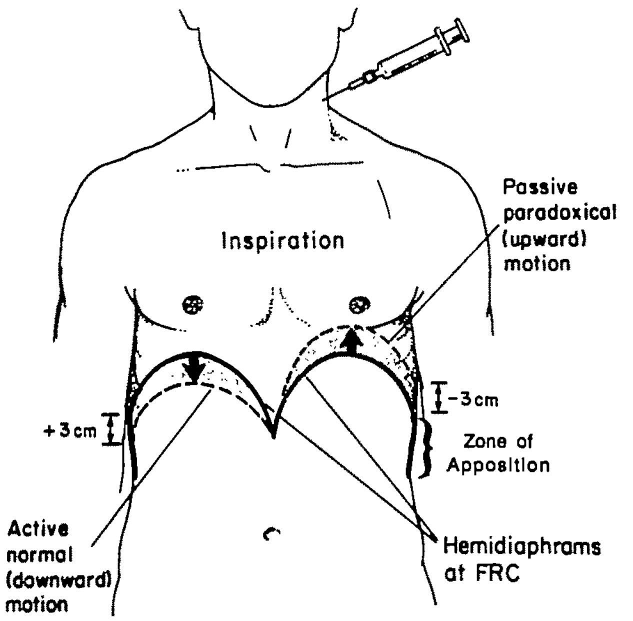

Inspiration
Passive paradoxical (upward) motion
-3cm
+3cm
Zone of Apposition
Active normal (downward) motion
Hemidiaphrams at FRC

Figure 1. Changes in hemidiaphragmatic excursion after typical left interscalene block. During inspiration the contralateral hemidiaphragm continues to exhibit normal active downward motion, while the paretic ipsilateral hemidiaphragm is passively moved upward by the decreasing pleural pressure. Typical hemidiaphragmatic excursions of +3 cm and −3 cm can be measured by ultrasonography of the zone of apposition (Z_{ap}) of diaphragm to rib cage.

of the cephalad border of the zone of apposition (Z_{ap}) of diaphragm to rib cage (10) was used as a potentially more sensitive method for diagnosing hemidiaphragmatic paresis (Figure 1).

Methods

Sixteen healthy patients (ASA I and II) scheduled for elective upper extremity surgery who were free of significant pulmonary symptoms or disease were studied. Data were collected on 13 consecutive patients scheduled for interscalene brachial plexus anesthesia. This was followed by data collection on three additional consecutive patients undergoing axillary brachial plexus block to evaluate hemidiaphragmatic function in patients having brachial plexus block without sensory anesthesia extending to the cervical area. Approval was obtained from the Institutional Review Board of the Hospital for Special Surgery, and written informed consent was given by each patient studied.

Patients received no premedication. In all patients, brachial plexus block was produced by injection of 34–52 mL 1.5% mepivacaine with 5 μg/mL epinephrine and 0.05 mEq/mL sodium bicarbonate. Local anesthetic volume was decided on by the attending anesthesiologist based on clinical criteria and experience. Patients were monitored with a pulse oximeter, and oxygen was administered by nasal cannulae at all times except during data collection.

Interscalene block was performed using single paresthesia technique with the needle tip at or caudad to cricoid level, as described by Winnie (1). Axillary block was done by transarterial technique without paresthesia. With both techniques, a 23-gauge, 2.5-cm needle was used.

Data were collected before and 2, 5, and 10 min after completion of interscalene local anesthetic injection. In addition, when possible (11 of 13 patients with interscalene block), measurements were made at hourly intervals in the recovery room after completion of surgery. In patients with axillary block, data were recorded 2, 5, 10, 15, 20, 25, and 30 min after injection. Dermatomal distribution of sensory anesthesia was determined by pinprick 10 min after interscalene or axillary injection.

Ipsilateral and contralateral hemidiaphragmatic excursions were measured by real-time ultrasonography (Diasonics DRF400, 3 MHz transducer) of the cephalad border of the zone of apposition of diaphragm to rib cage (Z_{ap}) between midclavicular and anterior axillary lines. All measurements were made with the patient in the supine position. Hemidiaphragmatic excursion was defined as the difference between the cephalad border of Z_{ap} at functional residual capacity and at end-inspiration or inspiratory maneuver. Excursion distance was expressed in centimeters from the functional residual capacity position. Normal inspiratory caudad diaphragmatic excursion was designated positive (+) motion and paradoxical cephalad motion negative (−) motion.

Diaphragmatic excursion was measured during quiet inspiration, deep inspiration, forceful sniff, and Mueller maneuver to −20 cm H_2O pressure by manometer. In seven patients, maximum inspiratory force was recorded immediately before and 10 min after local anesthetic injection. Results are expressed as mean ± standard deviation (SD). Statistical comparison of baseline ipsilateral hemidiaphragmatic excursions with those during anesthesia was done by Student's paired *t*-test. $P < 0.05$ was regarded as being statistically significant.

Results

Both forms of brachial plexus block resulted in satisfactory upper extremity anesthesia in every case. In no case was general anesthesia or supplementation

Table 1. Interscalene Block Patients: Ipsilateral and Contralateral Hemidiaphragmatic Excursion During Forceful Sniff

Patient No.	Age (yr)	Weight (kg)	Anesthetic volume (mL)	Cephalad sensory level	Contralateral hemidiaphragmatic motion at 5 min (cm)	Ipsilateral hemidiaphragmatic motion (cm) Baseline	2 min	5 min	10 min	Return to normal motion (h)
1	21	90	52	C-3	3.21	3.06	−3.68	−2.10	−3.21	3–4
2	21	57	34	C-3	6.4	10.54	−5.51	−6.94	−8.91	3–4
3	41	91	42	C-3	5.31	5.22	−4.16	−5.41	−2.63	3–4
4	60	60	42	C-2	4.64	4.83	−4.36	−5.22	−6.70	3–4
5	25	80	42	C-3	8.48	6.56	−4.45	−3.88	−5.03	3–4
6	27	75	45	C-3	5.07	5.65	−4.31	−3.97	−3.68	NM
7	27	80	50	C-4	6.66	5.46	−4.74	−5.27	−4.64	3–4
8	24	76	50	C-4	8.52	7.37	−4.31	−4.40	−2.97	3–4
9	61	52	36	C-4	5.22	6.13	+4.21	−3.40	−3.68	3–4
10	31	58	41	C-3	7.66	8.09	−3.88	−4.45	−4.07	4–5
11	32	59	39	C-2	7.37	6.27	−6.25	−3.54	−3.64	3–4
12	23	77	45	C-3	3.78	4.07	+5.41	−3.25	−6.70	NM
13	73	75	45	C-4	3.21	4.21	−3.06	−3.59	−3.01	3–4

NM, not measured because of patient discharge.

necessary. No sedatives were administered until 20 min after local anesthetic injection and only after completion of all data collection (with the exception of the postoperative offset data). There were no anesthetic complications in any of the patients who received brachial plexus block in our study.

Interscalene Block

Changes from normal (caudad) to paradoxical (cephalad) motion of the ipsilateral hemidiaphragm (IH) were seen in all 13 patients during sniff (Table 1) or Mueller maneuver within 5 min, and in 11 of 13 patients within 2 min, of anesthetic injection. Contralateral hemidiaphragmatic normal directional motion was always concomitantly preserved. Forceful sniff was the most quantitatively reproducible diagnostic maneuver. Mean diaphragm excursions during forceful sniff are shown graphically as a function of time after interscalene block in Figure 2. During sniff, mean baseline ipsilateral hemidiaphragmatic excursion was +5.96 ± 1.94 cm for the 13 patients. Mean baseline contralateral hemidiaphragmatic excursion was +5.81 ± 1.86 cm. At 2 min after anesthesia, mean ipsilateral hemidiaphragmatic excursion was −3.01 ± 3.57 cm; at 5 min, −4.26 ± 1.23 cm; and at 10 min, −4.53 ± 1.86 cm. Statistically significant decreases in ipsilateral hemidiaphragmatic excursion occurred between preanesthesia values and those at 2, 5, and 10 min by paired *t*-test ($P = 0.0001$), but not when values between 2 and 5 or 10 min were compared, nor did statistically significant changes in mean excursion occur between 5 and 10 min.

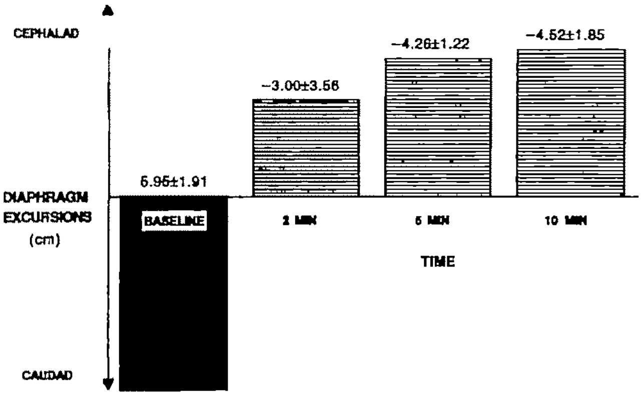


Figure 2. Ipsilateral hemidiaphragmatic excursions measured during sniff immediately before and 2, 5, and 10 min after interscalene local anesthetic injection. Positive (+) values and downward bar graph (baseline) represent normal (caudad) ipsilateral hemidiaphragmatic motion. This changed to negative (−) mean values, depicted by upward bar graph, representing paradoxical (cephalad) hemidiaphragmatic motion within 2 min. Mean hemidiaphragmatic excursion became progressively more paradoxical at 5 or 10 min after injection. Differences between baseline values and those at 2, 5, or 10 min were statistically significant ($P = 0.0001$).

Quiet or deep breathing resulted in similar decreases in ipsilateral hemidiaphragmatic excursion, but these maneuvers were less sensitive or consistent. During quiet breathing, normal ipsilateral diaphragmatic motion changed to paradoxical motion in 12 of 13 patients at 5 min. During deep breathing, all 13 patients had ipsilateral paradoxical hemidiaphragmatic motion at the beginning of inspiration at 5 min after injection. However, all 13 patients could overcome paradoxical hemidiaphragmatic motion initially present in every breath by continued deeper inspiration (see Discussion). In patients in whom maximum inspiratory force was measured, results were not reproducible and variations in effort were subjectively observed despite coaching.

Postoperatively, ipsilateral hemidiaphragmatic motion during sniff returned to normal in 10 of 11 patients between 3 and 4 h, and in the remaining one patient, within 5 h of anesthetic injection (Table 1).

All 13 patients had cervical sensory levels of anesthesia to pinprick. The most cephalad anesthetic sensory dermatome for each patient is displayed in Table 1. The contralateral side had normal sensation and no evidence of epidural anesthesia was found on either side by pinprick examination. Upon questioning, only 5 of 13 patients who underwent interscalene block noticed any change in breathing. This occurred despite the fact that all patients were unsedated and all had easily diagnosed hemidiaphragmatic paresis. Changes described were mild dyspnea or alterations in normal breathing sensations.

Axillary Block

None of the three patients showed significant changes in hemidiaphragmatic motion by ultrasound. No patient had sensory anesthesia to pinprick in the cervical dermatomes. None of the patients who had axillary blocks noticed any respiratory effect.

Discussion

One hundred percent of patients with interscalene brachial plexus anesthesia developed ipsilateral hemidiaphragmatic paresis detected by ultrasonography. This paresis was evidenced by change of hemidiaphragmatic directional motion from normal (caudad) to paradoxical (cephalad) during forceful sniff. Termination of motor blockade within 3–5 h was diagnosed by return to caudad motion using ultrasonography in all 11 patients who were studied postoperatively. This agrees with published reports of the duration of mepivacaine/epinephrine anesthesia (11). Return of normal diaphragmatic directional motion correlated with regression of upper extremity motor block on physical examination although this was not systematically assessed.

Shaw found an 80% incidence of hemidiaphragmatic paresis accompanying routine supraclavicular brachial plexus anesthesia when fluoroscopy was used during spontaneous inspiration (5). However, neither injection nor fluoroscopic techniques were well described in this study. Another study reported a 67% incidence of ipsilateral hemidiaphragmatic paresis with supraclavicular block when fluoroscopy was used during sniffing (6). In each of these studies, less local anesthetic volume and more caudad points of injection were usually used, and this may help to explain the lower incidence of cervical plexus anesthesia that developed. To ensure adequate cervical sensory anesthesia for shoulder surgery, we used local anesthetic volumes on average larger than those reported in the above studies (34–52 mL; mean, 43.3 ± 5.4 mL). Large anesthetic doses may in part account for the observed 100% incidence and relatively rapid onset of hemidiaphragmatic paresis. However, we have since injected smaller doses in many patients but have yet to produce cervical sensory anesthesia without accompanying hemidiaphragmatic paresis as detected by ultrasound during forceful sniff at 5 min after injection. A more probable explanation is that fluoroscopy during spontaneous inspiration and possibly during sniff may be a less sensitive technique for diagnosing hemidiaphragmatic paradoxical motion than are serial ultrasonographic examinations of the Z_{ap} during sniff. However, the two diagnostic methods and maneuvers have yet to be compared.

In a recent report of three patients who underwent perivascular subclavian brachial plexus anesthesia (12), two developed paradoxical hemidiaphragmatic motion during inspiration diagnosed by a double-exposure technique using superimposed chest radiographs. The authors pointed out that this technique offered the advantages of practicality and decreased radiation exposure when compared with fluoroscopy. But ultrasound involves no exposure to radiation. It is a technique that has previously been used to identify the cephalad border of the Z_{ap} in animals (13) and humans (10) and that can be used to quantify diaphragm excursion during breathing (14). It has been used previously to diagnose hemidiaphragm paresis in a pathological setting (15,16). Ultrasonography of the Z_{ap} is technically simple to perform and to interpret in addition to being free of radiation exposure.

Unilateral hemidiaphragmatic paresis may occur without respiratory symptoms (6,12). Five of our 13 patients who received interscalene anesthesia, however, complained of mild dyspnea or altered respiratory sensations. This was discovered on careful questioning in completely unsedated patients. However, we selected patients without significant preexisting respiratory disease. It is possible that this yielded a lower incidence of respiratory symptoms than might have been seen if patients with respiratory disease were included in the study. When there is preexisting respiratory system pathology, more marked changes in ventilation might occur. Figure 3 shows chest radiographs of a patient with scoliosis who under-

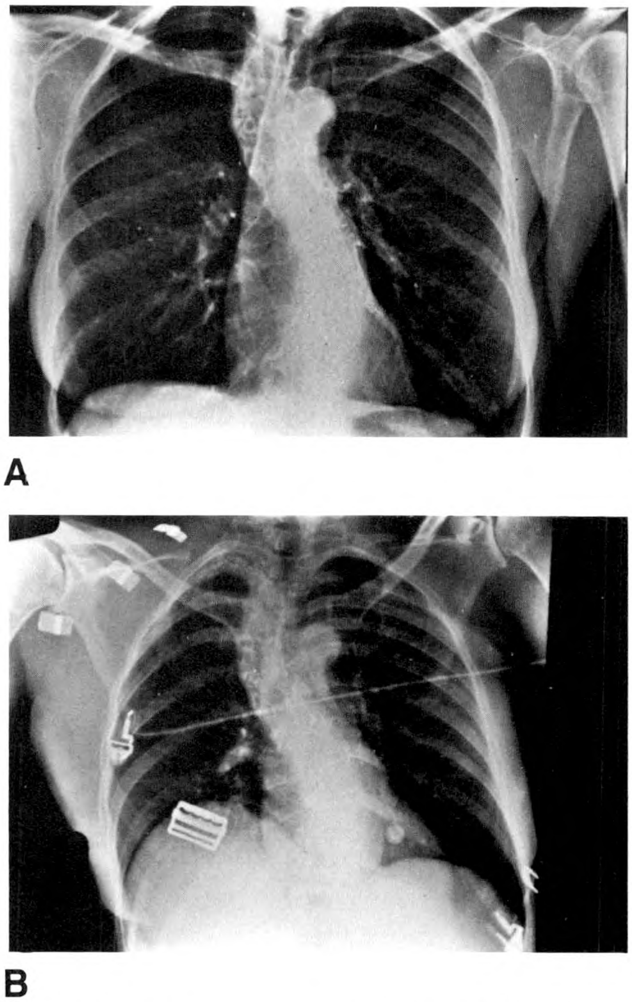


Figure 3. Chest radiographs from a patient with scoliosis before (**A**) and during (**B**) right interscalene brachial plexus anesthesia. During anesthesia, elevation of the right hemidiaphragm was evident.

went elective right shoulder arthroscopy in the sitting position during right interscalene brachial plexus anesthesia with 45 mL 1.5% mepivacaine with 5 μg/mL epinephrine and 0.05 mEq/mL bicarbonate. This patient had no complaints of dyspnea, but intraoperative auscultation revealed markedly diminished breath sounds in the right lower lung field, and ultrasonographic examination revealed paradoxical right hemidiaphragmatic motion during inspiration. Radiographic examination done in the recovery room to rule out pneumothorax revealed an elevated ipsilateral hemidiaphragm.

Ipsilateral hemidiaphragmatic paresis has been discussed as a "complication" (5,6,12) of interscalene block. Our data do not support this terminology. Rather than a complication, hemidiaphragmatic paresis should be thought of as an expected sequela of routine clinical interscalene brachial plexus anesthesia and should be planned for, just as a sympathetic block is not a complication but rather is anticipated during spinal anesthesia. In all 13 of our patients, deep enough inspirations during interscalene anesthesia always resulted eventually in normal downward ipsilateral hemidiaphragmatic excursion, even though paradoxical motion was seen with tidal breathing or at the beginning of the deep breath. This may have resulted from some remaining ipsilateral hemidiaphragmatic muscle activity, but it more probably represents a secondary phenomenon resulting from preserved contralateral hemidiaphragmatic and other inspiratory muscle actions. Our study cannot answer this question because we did not perform electromyographic studies of the hemidiaphragms. Even in patients with complete bilateral diaphragmatic paralysis, inspiration is associated with increased rib cage expansion relative to abdominal expansion during tidal breathing (8,16). The clinical importance of this is that all patients qualitatively had the ability to expand the ipsilateral lung despite the hemidiaphragmatic paresis that resulted from interscalene brachial plexus anesthesia. This helps to explain why interscalene or supraclavicular blocks have been done for years without invariable development of ipsilateral pulmonary atelectasis in every patient.

In our study, partial diaphragmatic paralysis was not always heralded by respiratory symptoms. Acute respiratory failure developing subsequent to interscalene block has, however, been attributed to diaphragmatic paresis (4). For this reason, as well as because of the recognized incidence of pneumothorax, techniques for providing upper extremity regional anesthesia by local anesthetic injection cephalad to the clavicle are relatively contraindicated in patients with respiratory disease (17). The above information may allow for better selection of these patients for interscalene block. Clinicians should expect unavoidable ipsilateral hemidiaphragmatic paresis with this technique and possibly rule out this anesthetic option when anesthetizing patients likely to need bilaterally intact diaphragmatic function. This includes patients with preexisting contralateral hemidiaphragmatic paresis, severe chronic obstructive pulmonary disease, or ankylosing spondylitis, in which rib cage motion is restricted (18,19). The data on duration of diaphragmatic paresis may serve as a guide for patient discharge from the postanesthetic care unit after interscalene block. Our results reinforce the importance of pulse oximetry as an adjunct to patient care during and immediately after regional anesthetics.

In addition, the present data have implications for deep cervical plexus anesthesia used for carotid artery surgery. The incidence of diaphragmatic paresis during this form of anesthesia also should be evaluated.

Finally, the 100% incidence of ipsilateral hemidiaphragmatic paradoxical motion, an all-or-nothing phenomenon, coupled with reproducible onset and offset, may make this a useful model for assessing local-anesthetic motor nerve blocking properties. Ultrasonographic detection of cervical motor nerve anesthesia occurred in 11 of 13 patients within 2 min of injection. This onset was faster than that reported for upper extremity anesthesia when conventional assessment of sensory and motor nerve function was done (11,20). Times from anesthetic injection to earliest detection of paradoxical hemidiaphragmatic motion by ultrasound may prove to be an easily accomplished, reproducible quantitative measurement of motor block onset.

The authors thank Susan Schraft, MD, for advice regarding ultrasonographic technique, Dawna S. Muratti and Nidia Rodriguez for careful preparation of the manuscript, and Marianne McDonald for technical assistance.

References

1. Winnie AP. Interscalene brachial plexus block. Anesth Analg 1970;49:455–66.
2. Seltzer JL. Hoarseness and Horner's syndrome after interscalene brachial plexus block. Anesth Analg 1977;56:585–6.
3. Ward ME. The interscalene approach to the brachial plexus. Anaesthesia 1974;29:147–57.
4. Hood J, Knoblanche G. Respiratory failure following brachial plexus block. Anaesth Intensive Care 1979;7:346–9.
5. Shaw WM. Paralysis of the phrenic nerve during brachial plexus anesthesia. Anesthesiology 1949;10:627–8.
6. Knoblanche GE. The incidence of aetiology of phrenic nerve blockade associated with supraclavicular brachial plexus block. Anaesth Intensive Care 1979;7:346–9.
7. Dhuner KG, Moberg E, Onne L. Paresis of the phrenic nerve during brachial plexus block analgesia and its importance. Acta Chirug Scand 1955;109:53–7.
8. Kreitzer SM, Feldman NT, Saunders NA, Ingram RH. Bilateral diaphragmatic paralysis with hypercapnic respiratory failure. Am J Med 1978;65:89–95.
9. Loh L, Goldman M, Davis JN. The assessment of diaphragm function. Medicine 1977;56:165–9.
10. Loring SH, Mead J, Griscom NT. Dependence of diaphragmatic length on lung volume and thoracoabdominal configuration. J Appl Physiol 1985;59:1961–70.
11. Covino BG, Vassallo HG. Local anesthetic mechanisms of action and clinical use. New York: Grune & Stratton, 1976:73.
12. Hickey R, Ramamurthy S. The diagnosis of phrenic nerve block on chest x-ray by a double-exposure technique. Anesthesiology 1989;70:704–7.
13. Urmey WF, De Troyer A, Kelly KB, Loring SH. Pleural pressure increases during inspiration in the zone of apposition of diaphragm to rib cage. J Appl Physiol 1988;65:2207–12.
14. Loring SH, Kurachek SC, Wohl MEB. Diaphragmatic excursion after pleural sclerosis. Chest 1989;95:374–8.
15. Diament MJ, Boechat MI, Kangarloo H. Real time sector ultrasound in the evaluation of suspected abnormalities of diaphragmatic motion. J Clin Ultrasound 1985;13:539–43.
16. Skatrud J, Iber C, McHugh W, Rasmussen H, Nicholas D. Determinants of hypoventilation during wakefulness and sleep in diaphragmatic paralysis. Am Rev Resp Dis 1980;121:587–93.
17. Moore DC. Regional block, 4th ed. Springfield, Ill.: Charles C. Thomas, 1975:240.
18. Feltelius N, Hedenstrom H, Hillerdal G, Hallgren R. Pulmonary involvement in ankylosing spondylitis. Ann Rheum Dis 1986;45:736–40.
19. Efthimiou J, McLelland J, Round J, Gibbin HR, Loh L, Spiro SG. Diaphragm paralysis causing ventilatory failure in an adult with the rigid spine syndrome. Am Rev Respir Dis 1987;136:1483–5.
20. Covino BG, Bush DF. Clinical evaluation of local anaesthetic agents. Br J Anaesth 1975;47:289–96.

Postoperative Neuromuscular Function in Pediatric Day-Care Patients

Michael R. N. Baxter, MB, FFARCS, Joan C. Bevan, MD, FFARCS, Jacob Samuel, MB, FFARCS, François Donati, MD, PhD, FRCPC, and David R. Bevan, MB, MRCP, FFARCS

BAXTER MRN, BEVAN JC, SAMUEL J, DONATI F, BEVAN DR. Postoperative neuromuscular function in pediatric day-care patients. Anesth Analg 1991;72:504–8.

After anesthesia employing nondepolarizing muscle relaxants, 30%–40% of adult patients demonstrate residual paralysis with a train-of-four ratio <70%, but it is not known if the same is true for children. This study was designed to investigate neuromuscular transmission in 91 ASA physical status I or II day-care children (aged 0–10 yr) after halothane anesthesia in which pancuronium (n = 34), atracurium (n = 32), or vecuronium (n = 25) was administered. Peripheral nerve stimulation was used clinically to assess neuromuscular blockade during surgery. In the recovery room, the evoked response of the adductor pollicis muscle was measured by train-of-four stimulation of the ulnar nerve. This measurement was made (mean ± SEM) at 18.0 ± 1.5, 15.0 ± 1.3, and 15.0 ± 1.7 min after pharmacologic antagonism with 0.02 mg/kg atropine and 0.06 mg/kg neostigmine in the pancuronium, atracurium, and vecuronium groups, respectively. There were no differences in the ages of the patients in the three groups at 4.3 ± 0.4, 4.0 ± 0.4, and 5.0 ± 0.5 yr, with 17 children less than 2 yr. Recovery from neuromuscular blockade in all three groups was almost complete. The train-of-four ratio (height of fourth twitch compared with the first) was similar in patients who had received pancuronium (96.7% ± 0.9%), atracurium (95.5% ± 0.9%), or vecuronium (96.3% ± 1.3%). Therefore, postoperative muscle weakness or respiratory impairment is unlikely in pediatric day-care surgical patients more than 2 yr old when these anesthetic techniques are used.

Key Words: ANESTHESIA, PEDIATRIC. NEUROMUSCULAR RELAXANTS, ATRACURIUM, PANCURONIUM, VECURONIUM.

Residual neuromuscular blockade is common in adults after anesthesia using nondepolarizing neuromuscular blocking drugs (NMBDs). Pancuronium has been shown to be followed by postoperative weakness, with train-of-four (TOF) ratios <70% in 20%–40% of patients (1,2). In these studies relaxant dosage was determined clinically and often large doses were given. However, similar results were obtained using pancuronium in adults when neuromuscular monitoring with peripheral nerve stimulation with visual or tactile observation of thumb responses was used intraoperatively (3). The use of the shorter acting muscle relaxants was associated with less residual effect; the incidence of residual blockade being only 4% after atracurium (3,4) and 9% after vecuronium (3).

Furthermore, muscle weakness has been demonstrated for several hours after neostigmine reversal of pancuronium, atracurium, and vecuronium blockade in adults. When clinical responses were used to guide relaxant dosage, grip strength was impaired even when a head-lift could be sustained for 5 s after atracurium and pancuronium (5) and for more than 1 h after reversal of pancuronium, atracurium, or vecuronium (5,6). The use of peripheral nerve stimulation to monitor the depth of neuromuscular blockade during surgery and recovery before the administration of neostigmine to reverse atracurium or pancuronium blockade did not abolish these deficits postoperatively (7). In two of these studies (6,7), maximum inspiratory and expiratory force measurements were reduced to half of control values after surgery, despite clinically satisfactory breathing at the end of the procedure. Recovery to normal values took 1–3 h and was progressively longer for atracu-

---

Presented at the annual meeting of the Association of Paediatric Anaesthetists of Great Britain and Ireland, March 1989.

Received from the Departments of Anesthesia, Montreal Children's Hospital, Royal Victoria Hospital, and McGill University, Montreal, Quebec, Canada. Accepted for publication November 21, 1990.

Address correspondence to Dr. Bevan, Department of Anesthesia, Montreal Children's Hospital, 2300 Tupper, Montreal, Quebec H3H 1P3, Canada.

Reprints will not be available from the authors.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

rium, vecuronium, and pancuronium (6,7). In some patients, residual diplopia and muscle weakness persisted for up to 24 h after administration of atracurium and vecuronium (6).

Pediatric units now perform as much as 80% of surgery on a day-care basis. Failure to recognize residual blockade in these patients could lead to their discharge from hospital while at risk of respiratory impairment. This study investigated neuromuscular transmission in children on arrival in the recovery room after halothane anesthesia that included pancuronium, atracurium, or vecuronium.

Patients and Methods

The study was conducted with the approval of the Hospital Institutional Review Board. Ninety-one children (aged 0–10 yr, and ASA physical status I or II) undergoing surgery as outpatients were studied.

The attending anesthesiologist was not informed that the study would be undertaken. None of the patients received premedicant drugs, and the anesthetic technique was at the discretion of the anesthesiologist. A retrospective review of the anesthetic records showed that all anesthesiologists used similar techniques of anesthesia. Induction of anesthesia with thiopentone (5–7 mg/kg) was followed by maintenance with 0.5%–1.0% halothane. Tracheal intubation was facilitated by succinylcholine (1–1.5 mg/kg) in 63% of patients and by the nondepolarizing agent in the remainder. Surgical relaxation was continued with intermittent doses of relaxants, using peripheral nerve stimulation of the adductor pollicis to monitor neuromuscular blockade. Visual and tactile assessments of the TOF response were used clinically, but the degree of recovery that determined the need for incremental doses of relaxants or the timing of extubation was not recorded. At the end of surgery, neuromuscular blockade was reversed with 0.02 mg/kg atropine and 0.06 mg/kg neostigmine before extubation. The patient was transferred to the recovery room when considered to be satisfactorily recovered clinically by the anesthesiologist.

When the anesthesiologist left the patient in the recovery room, those patients who had received nondepolarizing muscle relaxants (according to their anesthetic record) were selected for study. Neuromuscular transmission was then assessed using the evoked response of the adductor pollicis muscle to supramaximal stimulation of the ulnar nerve. Square pulses of 0.2-ms duration were delivered at a frequency of 2 Hz every 12 s. The patient's hand and forearm were immobilized in a splint, and the force of contraction of the adductor pollicis was measured with a Grass FT 03 force-displacement transducer and recorded on paper. When a stable recording was obtained, the ratio of the fourth to the first twitch height in the TOF (TOF ratio) was calculated. The children were monitored at various stages of awakening. Some response and movement on stimulation were seen, but the patients were not distressed and satisfactory recordings were obtained.

The duration of anesthesia, time between reversal of neuromuscular blockade and measurement of TOF response, and the total dose of relaxant given were recorded. Comparisons were made between groups of patients who had received pancuronium, atracurium, and vecuronium. Statistical analysis was carried out using χ^2 analysis and Student's *t*-test. Analysis of variance was used for comparisons of groups, and the Bonferroni correction was applied. Significant differences were found if the *P* value was ≤ 0.05.

Results

Ninety-one patients received nondepolarizing muscle relaxants. They were divided into three groups of patients who had received pancuronium, atracurium, or vecuronium (Table 1). There were no differences in the mean ages and weights of the patients in each group. Seventeen of the patients were under 2 yr old, and they were distributed among the groups as shown in Table 1. Of these, six were infants (<12 mo old), with the youngest aged 6 wk. Pancuronium was given to four infants and atracurium to two; no infant received vecuronium.

The total doses of pancuronium, atracurium, and vecuronium were 0.07 ± 0.01, 0.48 ± 0.05, and 0.11 ± 0.01 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, respectively. Succinylcholine was administered to 31 patients. The duration of surgery and anesthesia was significantly longer in the pancuronium than in either the atracurium or vecuronium group, but the time interval between reversal of blockade and TOF recording was similar in all three groups. The TOF ratios ranged from 80% to 100% with no significant differences among the groups.

Discussion

In contrast to adult experiences, none of the children studied showed residual neuromuscular blockade on arrival in the recovery room after anesthesia in which pancuronium, atracurium, or vecuronium was given. Bevan et al. (3) found that 36%, 4.3%, and 8.8% of

Table 1. Demographic Data and Characteristics of Neuromuscular Blockade

	Relaxant		
	Pancuronium	Atracurium	Vecuronium
n	34	32	25
Number < 2 yr	8	7	2
Age (yr)	4.3 ± 0.4	4.0 ± 0.4	5.0 ± 0.5
Weight (kg)	17.1 ± 0.9	16.3 ± 0.9	19.0 ± 1.0
Succinylcholine (*n*)	31	15	11
Relaxant dose ($mg \cdot kg^{-1} \cdot h^{-1}$)	0.07 ± 0.01	0.48 ± 0.05	0.11 ± 0.01
Duration of surgery (min)	100.0 ± 9.0[a]	76.0 ± 8.0	77.7 ± 7.0
Interval between neostigmine and TOF monitoring (min)	18.0 ± 1.5	15.0 ± 1.3	15.0 ± 1.7
TOF ratio (%)	96.7 ± 0.9	95.5 ± 0.9	96.3 ± 1.3

TOF, train-of-four.
Values are expressed as mean ± SEM.
[a] $P < 0.05$ versus atracurium and vecuronium groups.

adults demonstrated TOF ratios <70% after pancuronium, atracurium, and vecuronium, respectively (3). As neuromuscular blockade was monitored in similar ways by peripheral nerve stimulation in all of the children and 74% of the adults, the discrepancy between the findings in adults and children requires further explanation.

The adults provided a heterogenous group of hospitalized general surgical patients, whereas the children were a more homogenous group of healthy day-care patients undergoing superficial operations. The duration of surgery was about 50% longer in the adults than in the children in all three relaxant groups. Anesthesia was more varied in the adults and included premedication and supplementation of anesthesia with fentanyl, enflurane, or isoflurane, whereas the children received only halothane.

The higher dose requirements (pancuronium 0.07 vs 0.03, atracurium 0.48 vs 0.37, and vecuronium 0.11 vs 0.06 $mg \cdot kg^{-1} \cdot h^{-1}$) with more complete recovery from paralysis in the children may be due to their different clinical circumstances, or may result from age-related differences in response to NMBDs and their antagonists. Recently, it has been demonstrated that the potency, rate of spontaneous recovery, and speed of pharmacologic reversal of the nondepolarizing relaxants in children differ from those in adults.

Children appear to require higher doses of nondepolarizing relaxants than adults to produce the same effect, although none of the estimates for potency at different ages have been obtained under identical conditions of anesthesia and monitoring. The ED_{95} doses in children (aged 1–10 yr) are higher than in adults during halothane and balanced anesthesia for pancuronium (0.05–0.06 mg/kg) (8,9), atracurium (0.15–0.32 mg/kg) (10–13), and vecuronium (0.06–0.08 mg/kg) (14,15). The responses are variable in infants, but most studies show that values in infants are similar to those in adults (9,12,13,15) and smaller than in older children. In the present study, most patients were between 2 and 10 yr old so that larger doses were needed to maintain surgical relaxation compared with the adults. However, the hourly maintenance doses in the adults were reduced by different degrees in the children: pancuronium (57%), atracurium (23%), and vecuronium (45%). This suggests that the dose requirements might also be influenced by the cumulative effects of pancuronium (16) during longer procedures and by the absence of cumulation with atracurium (17).

The choice of inhalation agent affects the rate of spontaneous recovery. This may be important because halothane is commonly used in pediatric, but not adult, anesthesia. Enflurane, which was frequently used in the adult study, prolongs recovery from neuromuscular blockade (18–22) so that impaired neuromuscular function for longer is more likely. Most studies have demonstrated similar rates of recovery from pancuronium, atracurium, and vecuronium neuromuscular blockade in children and adults (8,10,11). There are some reports of shorter recovery indices (RI), from 25% to 75% first twitch recovery (11.1–14.0 min for atracurium and 7.9–9.1 min for vecuronium), in children (10,11,14,22) compared with adults. Halothane prolongs the RI of atracurium by 25% (11) but does not alter the RI of vecuronium, compared with fentanyl, in children (14,23). One study found that the RI of atracurium is longer after the first dose in adults, but shorter after a second dose (16.1 min) than the RI of vecuronium (19.8 min) (24). In infants, the RI for vecuronium is prolonged to 21 min (25) but is shortened for atracurium to 8 min (10) compared with older children. As most of the children in the present study were older than 2 yr and were anesthetized with halothane, a more rapid recovery was expected than in adults.

The use of larger doses of neostigmine (0.06 mg/kg) in the children, compared with more modest doses in the adult studies (1–7) (approximately 0.03 mg/kg), is likely to be an important determinant of the rapidity of recovery of normal neuromuscular function in the children. Despite the acceptance of the use of neostigmine in doses up to 0.07 mg/kg to prevent respiratory depression postoperatively in children (26), reversal of neuromuscular blockade with anticholinesterases is more rapid and requires smaller doses of neostigmine and edrophonium in children than in adults (27–30). Reversal of pancuronium blockade with neostigmine is dose dependent; when 0.036- and 0.071-mg/kg doses were used, recovery was more rapid in children than in adults at both doses, and recovery was almost complete in the children in 10 min, but 30 min was required before the adults recovered to the same extent (27). When vecuronium blockade was reversed with neostigmine (0.03 mg/kg in children and 0.04 mg/kg in adults), the rate of recovery was more rapid in children than in adults (30). The extent of reversal achieved by neostigmine is not the same for each relaxant. Ten minutes after its administration, the ED_{80} for neostigmine is lower for atracurium (0.022 mg/kg) than for vecuronium (0.024 mg/kg) and pancuronium (0.045 mg/kg) in adults (29). Volatile agents, especially enflurane, impair antagonism of neuromuscular blockade more in adults than children (23,31–33). In this study, muscle relaxants were given with the help of peripheral nerve stimulation so that complete or intense block, which could alter the rate of antagonism (34), was avoided. Thus, rapid reversal of the block was expected.

In conclusion, there are several reasons why recovery from neuromuscular blockade is more rapid in children than adults. These include decreased potency of relaxants, more rapid spontaneous recovery, and more rapid reversal. In addition, volatile agents such as enflurane and isoflurane, which potentiate neuromuscular block, prolong recovery, and impair reversal, are commonly used in adult anesthesia. They are usually replaced with halothane, which has less influence on NMBDs, in pediatric anesthesia. The results of the present study support such a hypothesis and suggest that residual weakness after the use of NMBDs during anesthesia is uncommon in children. Such rapid and complete recovery of neuromuscular function that was found in these day-care surgical patients support their use in this setting.

References

1. Viby-Mogensen J, Jorgensen BC, Ording H. Residual curarization in the recovery room. Anesthesiology 1979;50:539–41.
2. Anderson BN, Madsen JV, Schurizek BA, Juhl B. Residual curarization: a comparative study of atracurium and pancuronium. Acta Anaesthesiol Scand 1988;32:79–81.
3. Bevan DR, Smith CE, Donati F. Postoperative neuromuscular blockade: a comparison between atracurium, vecuronium, and pancuronium. Anesthesiology 1988;69:272–6.
4. Howardy-Hansen P, Rasmusen JA, Jensen BN. Residual curarization in the recovery room: atracurium versus gallamine. Acta Anaesthesiol Scand 1989;33:167–9.
5. O'Connor M, Russell WJ. Muscle strength following anaesthesia with atracurium and pancuronium. Anaesth Intensive Care 1988;16:255–9.
6. Kong KL, Cooper GM. Recovery of neuromuscular function and postoperative morbidity following blockade by atracurium, alcuronium and vecuronium. Anaesthesia 1988;43:450–3.
7. Hutton P, Burchett KR, Madden AP. Comparison of recovery after neuromuscular blockade by atracurium or pancuronium. Br J Anaesth 1988;60:36–42.
8. Goudsouzian NG, Ryan JF, Savarese JJ. The neuromuscular effects of pancuronium in infants and children. Anesthesiology 1974;41:95–8.
9. Laycock JRD, Baxter MRN, Bevan JC, Sangwan S, Donati F, Bevan DR. The potency of pancuronium at the adductor pollicis and diaphragm in infants and children. Anesthesiology 1988;68:908–11.
10. Brandom BW, Woelfel SK, Cook DR, Fehr BL, Rudd GD. Clinical pharmacology of atracurium in infants. Anesth Analg 1984;63:309–12.
11. Goudsouzian NG, Liu LMP, Gionfriddo M, Rudd GD. Neuromuscular effects of atracurium in infants and children. Anesthesiology 1985;62:75–9.
12. Meakin G, Shaw EA, Baker RD, Morris P. Comparison of atracurium-induced neuromuscular blockade in neonates, infants and children. Br J Anaesth 1988;60:171–5.
13. Meretoja OA, Wirtavuori K. Influence of age on the dose-response relationship of atracurium in paediatric patients. Acta Anaesthesiol Scand 1988;32:614–8.
14. Goudsouzian NG, Martyn JJA, Liu LM, Gionfriddo M. Safety and efficacy of vecuronium in adolescents and children. Anesth Analg 1983;62:1083–8.
15. Meretoja OA, Wirtavuori K, Neuvonen PJ. Age-dependence of the dose-response curve of vecuronium in pediatric patients during balanced anesthesia. Anesth Analg 1988;67:21–6.
16. Fahey MR, Morris RB, Miller RD, Sohn YJ, Cronnelly R, Gencarelli P. Clinical pharmacology of ORG NC45 [Norcuron]: a new nondepolarizing muscle relaxant. Anesthesiology 1981;55:6–11.
17. Payne JP, Hughes R. Evaluation of atracurium in anaesthetized man. Br J Anaesth 1981;53:45–54.
18. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI. The dependence of pancuronium- and *d*-tubocurarine-induced neuromuscular blockades on alveolar concentrations of halothane and forane. Anesthesiology 1972;37:573–81.
19. Rupp SM, McChristian JW, Miller RD. Neuromuscular effects of atracurium during halothane-nitrous oxide and enflurane-nitrous oxide anesthesia in humans. Anesthesiology 1985;63:16–9.
20. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. Anesthesiology 1984;60:102–5.

21. Swen J, Rashkovsky OM, Ket JM, Koot HJ, Hermans J, Agoston S. Interaction between nondepolarizing neuromuscular blocking agents and inhalational agents and inhalational anesthetics. Anesth Analg 1989;69:752–5.

22. Eriksson LI, Staun P, Lennmarken C. The influence of 0.5% isoflurane on a vecuronium-induced neuromuscular blockade. Acta Anaesthesiol Scand 1989;33:309–12.

23. Pittet JF, Melis A, Rouge JC, Gemperle G, Morel DR, Tassoni E. Effect of volatile anesthetics on vecuronium-induced neuromuscular blockade in children. Anesthesiology 1990;70:248–52.

24. Erkola O, Karhunen U, Sandelin-Hellqvist E. Spontaneous recovery of residual neuromuscular blockade after atracurium or vecuronium during isoflurane anaesthesia. Acta Anaesthesiol Scand 1989;33:290–4.

25. Kalli I, Meretoja OA. Duration of action of vecuronium in infants and children anaesthetized without potent inhalational agents. Acta Anaesthesiol Scand 1989;33:29–33.

26. Cook DR. Muscle relaxants in infants and children. Anesth Analg 1981;60:335–43.

27. Meakin G, Sweet PT, Bevan JC, Bevan DR. Neostigmine and edrophonium as antagonists of pancuronium in infants and children. Anesthesiology 1983;59:316–21.

28. Fisher DM, Cronnelly R, Miller RD, Sharma M. The neuromuscular pharmacology of neostigmine in infants and children. Anesthesiology 1983;59:220–5.

29. Smith CE, Donati F, Bevan DR. Dose-response relationships for edrophonium and neostigmine as antagonists of atracurium and vecuronium neuromuscular blockade. Anesthesiology 1989;71:37–43.

30. Debaene B, Meistelman C, d'Hollander A. Recovery from vecuronium neuromuscular blockade following neostigmine administration in infants, children, and adults during halothane anesthesia. Anesthesiology 1989;71:840–4.

31. Dernovci B, Agoston S, Barvais L, Baurain M, Lefebvre R, d'Hollander A. Neostigmine antagonism of vecuronium paralysis during fentanyl, halothane, isoflurane, and enflurane anesthesia. Anesthesiology 1987;66:698–701.

32. Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. Br J Anaesth 1982;54:441–5.

33. Fisher DM, Miller RD. Neuromuscular effects of vecuronium (ORG NC45) in infants and children during N_2O, during halothane anaesthesia. Anesthesiology 1983;58:519–23.

34. Meistelman C, Debaene B, d'Hollander A, Donati F, Saint-Maurice C. Importance of the level of paralysis recovery for a rapid antagonism of vecuronium with neostigmine in children during halothane anesthesia. Anesthesiology 1988;69:97–9.

ANESTH ANALG 509
1991;72:509–15

Sensory and Motor Blockade During Epidural Analgesia With 1%, 0.75%, and 0.5% Ropivacaine—A Double-Blind Study

Dusanka Zaric, MD, Kjell Axelsson, MD, PhD, Per-Anders Nydahl, MD, PhD,
Lennart Philipsson, PhD, Pål Larsson, MD, and Jan Robert Jansson, MD

ZARIC D, AXELSSON K, NYDAHL P-A, PHILIPSSON L, LARSSON P, JANSSON JR. Sensory and motor blockade during epidural analgesia with 1%, 0.75%, and 0.5% ropivacaine—a double-blind study. Anesth Analg 1991;72: 509–15.

Levels of sensory (pinprick) and somatic motor blockade were measured in a double-blind study of 30 volunteers given single epidural injections of 1%, 0.75%, and 0.5% ropivacaine. Onset of analgesia was rapid with all concentrations (7–10 min). Maximal levels of analgesia were established 60 min after injection, with no significant differences in the maximal median cephalad spread. Duration of analgesia at the T-12 level and total duration were significantly longer with 1% and 0.75% than with 0.5% ropivacaine. Motor blockade was assessed by a quantitative method (measurements of isometric muscle force) and a qualitative method (modified Bromage scale). Onset of motor blockade measured by the quantitative method was significantly slower with 0.5% ropivacaine than with the higher concentrations. Maximal muscle weakness occurred 1–1.5 h after injection with all three concentrations. With increase in ropivacaine dose from 100 to 200 mg, the intensity and duration of motor blockade increased. Muscles involved in knee extension were blocked most, those of plantar flexion least. Recovery of motor function, assessed by the above-mentioned quantitative method, occurred simultaneously with the recovery of pinprick perception. Motor blockade registered by Bromage scale showed a slower onset for 0.5% ropivacaine than for the higher concentrations. Mean durations of grade 1 and 2 block were longest for the 1% solution. Motor blockade described by the Bromage scale showed only the first part of the regression phase. Full recovery of muscle strength (Bromage scale = 0) was attained 1.5–2.5 h earlier than assessed by the quantitative method. No adverse effects were registered.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—ropivacaine. ANESTHETICS, LOCAL—ropivacaine.

Ropivacaine (LEA 103) is a recently introduced long-acting amino-amide local anesthetic, a congener to bupivacaine and mepivacaine. Recent clinical studies have shown that in humans 0.5% ropivacaine and 0.5% bupivacaine are comparable when used for brachial plexus or epidural blockade (1). Preliminary reports about the properties of ropivacaine in epidural anesthesia on small numbers of patients have been controversial. Some authors found no differences between different concentrations (2), whereas others showed that the increase in ropivacaine concentration prolonged the duration of sensory and motor blockade (3). In these studies, motor blockade was assessed only by Bromage scale, which is qualitative in its nature. Quantitative methods for measuring isometric muscle force give precise descriptions of duration and degree of motor blockade (4,5). It is therefore of interest to use both methods in the evaluation of the new local anesthetic.

This study was undertaken, first, to determine sensory and motor blockade profiles for 1%, 0.75%, and 0.5% ropivacaine given epidurally; second, to compare motor blockade evaluated by two methods (the Bromage scale and quantitative measurements of muscle force); and, third, to relate to each other the levels of sensory and motor blockade.

Materials and Methods

Thirty healthy male volunteers, 10 in each group (Table 1), participated in the study after informed consent had been obtained. The study was randomized, double-blind, and approved by the Ethics Com-

---

Received from the Departments of Anesthesiology and Intensive Care and Neurophysiology, Örebro Medical Center Hospital, Örebro; Department of Anesthesiology, Linköping University, Linköping; and Astra Pain Control AB, Södertälje, Sweden. Accepted for publication November 23, 1990.

Address correspondence to Dr. Zaric, Department of Anesthesiology and Intensive Care, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Characteristics of 30 Volunteers (10 in each group) Receiving Epidural Anesthesia

Local anesthetic	Age (yr)	Weight (kg)	Height (cm)
0.5% ropivacaine (100 mg)	28 ± 2.3	80 ± 2.2	181 ± 1.5
0.75% ropivacaine (150 mg)	27 ± 1.9	78 ± 2.9	180 ± 1.4
1.0% ropivacaine (200 mg)	27 ± 1.9	81 ± 1.8	186 ± 1.2

Values are mean ± SEM.

mittee of Örebro Medical Center Hospital. All subjects received 0.25 mg IV atropine at the start of the study. With the subject in the right lateral position, the epidural space was identified at the L2-3 level with a 16-gauge Tuohy needle using the loss of resistance method. A single injection of 20 mL ropivacaine 1% (200 mg), 0.75% (150 mg), or 0.5% (100 mg) was administered, 4 mL as a test dose followed by 16 mL 4 min later in the absence of evidence of intravascular or intrathecal injection. During the study 300–500 mL of Ringer's acetate solution was given intravenously.

Sensory blockade was registered bilaterally by the pinprick method with a blunt 27-gauge needle. It was applied on the midclavicular line in both cranial and caudal directions every 5 min during the first half hour and later simultaneously with other measurements. The onset of analgesia was expressed as the time taken to first evidence of sensory blockade of any spinal segment level.

Muscle force was measured by two methods: a modified Bromage scale (grades 0–3) as described elsewhere (5), and a quantitative method introduced earlier by one of the authors (6). The quantitative method required recording of baseline values for muscle force (100%) in each subject before the epidural injection was performed. This was done by registering five maximal isometric contractions in the lithotomy position (bilaterally) for knee extension (innervation from L2-4), hip flexion (L1-3), and plantar flexion of the big toe (L5-S1). These five measurements were repeated four times, and the average level of muscle strength was taken as baseline. This order (first knee, then hip, and last of all toe movement) was chosen because the onset of muscle blockade was expected to be most rapid for muscles involved in knee extension. After epidural injection the onset of motor blockade was assessed every 15 min until steady state was reached. During maximal motor blockade and in the regression phase, the measurements were carried out every half hour until 90% of the baseline muscle strength was reached in all tests of motor function.

A continuous time-course of motor blockade was estimated by interpolation. The onset was evaluated by comparison of the time needed to decrease muscle force to 75%, 50%, and 25% of the baseline value for each movement and concentration separately. In the same way regression of blockade was measured when 25%, 50%, 75%, and 90% of the baseline muscle strength for each concentration and movement had returned.

When 90% of the baseline muscle strength had returned, the subject was carefully mobilized—first to a sitting position, then to standing up on toes and heels, and last, to slow walking followed by jogging. The modified Bromage scale was applied at the same time intervals as quantitative measurements. The urinary bladder was checked for distention by palpation and percussion especially in cases of long-lasting blockade, and catheterization was performed if necessary. Blood pressure and electrocardiogram were recorded throughout the study.

The term "intensity" of motor blockade refers to the maximal muscle weakness that occurred between onset and the regression phase. "Maximal motor blockade duration" was expressed as the period of maximal muscle weakness + 10% of the baseline force (7).

Statistics

Measurements of sensory and motor blockade (quantitative method) were performed bilaterally, and the average value was taken as representative of both sides. When asymmetric motor blocks were registered by Bromage scale, the lower score was chosen. Interval variables (durations of sensory and motor blockades) are presented as mean ± SEM; ordinal variables (extent of analgesia) are presented as median (range). The Kruskal–Wallis test was used for evaluation of differences between the groups, followed by Wilcoxon's rank sum test where necessary. Wilcoxon's signed rank test was applied on paired data. $P < 0.05$ was accepted as the level of significance.

Results

Sensory Blockade

Onset of analgesia was rapid with all concentrations (7 ± 1.0 min for the 1% solution, 9 ± 0.9 min for the 0.75%, and 10 ± 1.2 min for the 0.5% solution; mean ± SEM). There were no differences in onset at various segments for different concentrations. No significant difference in maximal cranial spread was noticed: for

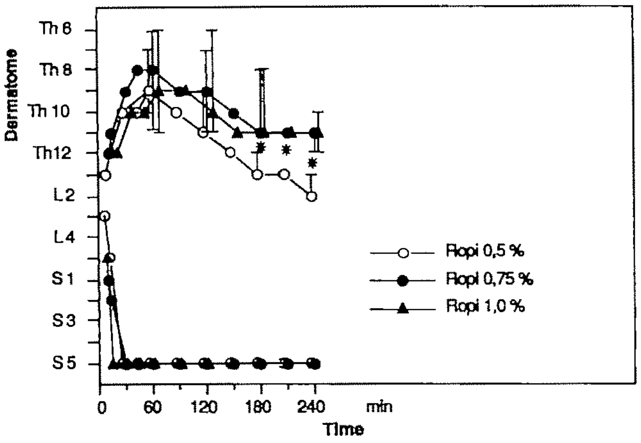


Figure 1. The segmental spread of epidural analgesia with different concentrations of ropivacaine (median ± lower and upper quartiles). *Spread of analgesia in the 0.5% group significantly less than that in the 0.75% and 1% groups.

the 1% solution the median value was T-9 (range T-4 to T-12), for 0.75% T-8 (T-3 to T-11), and for 0.5% ropivacaine T-10 (T-7 to T-12). Time taken to reach maximal spread (both caudal and cranial) averaged 60 min (Figure 1). There were no missing segments.

Time to two-segment regression of the cranial level of analgesia averaged 227 ± 27.2 min with 1%, 203 ± 20.3 min with 0.75%, and 167 ± 15.5 min with the 0.5% solution; differences were not statistically significant. The duration of analgesia at T-12 and all lumbar segments was significantly less with 0.5% ropivacaine; at sacral segments there were significant differences among all three concentrations (Figures 2a, 3a, and 4a). The total duration was less with the 0.5% solution than with higher concentrations (Table 2).

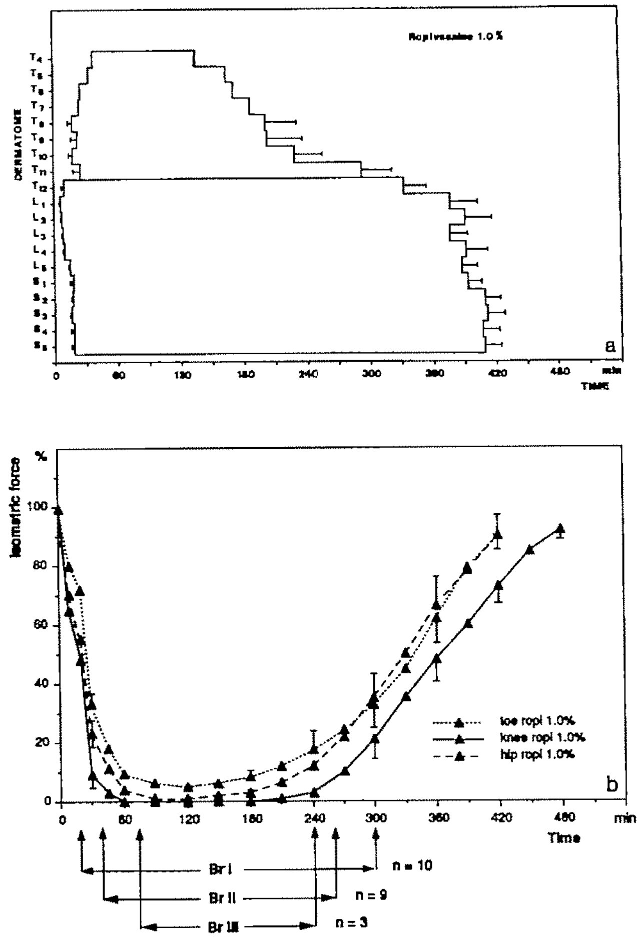


Figure 2. Onset, duration, and regression of sensory (a) and motor (b) epidural blockade with 1% ropivacaine in 10 volunteers (mean ± SEM). The *horizontal line* shows the level of analgesia achieved by all subjects. *Br I* refers to Bromage scale grade 1 and *n* to the number of subjects involved. There were no significant differences between movements in onset or regression.

Motor Blockade

Bromage scale. Times of onset, i.e., the time from epidural injection until Bromage grade 0 changed to grade 1, were similar in the 1% and 0.75% groups (18 vs 20 min), but significantly longer with 0.5% (27 min) than with 1% ropivacaine (Figures 2b, 3b, and 4b). Intense motor blockade (grade 3) developed in three subjects in the 1% ropivacaine group and in one subject in the 0.75% group. Six subjects in the 0.5% group had Bromage grade 1; the rest had grade 0. The mean duration of motor blockade for the Bromage grade 1 level was significantly longer with 1% than with 0.75% and 0.5% ropivacaine (Figures 2b and 3b, and Table 2). Even at grade 2 the duration of motor blockade was longer with 1% than with 0.75% ropivacaine.

Quantitative measurements. ONSET. When different movements were taken into consideration, the onset time for motor blockade was longest for plantar flexion of big toe (L5-S2) regardless of the concentration used (Figures 2b, 3b, and 4b). For example, in the 1% ropivacaine group, onset 50% (the time to 50% blockade) took 15 ± 1.2 min for knee extension and 23 ± 2.0 min for plantar flexion.

When the three concentrations were compared, onset of blockade was generally slower for all movements with 0.5% ropivacaine than with the 0.75% and 1% solutions. For example, hip flexion onset 50% came after 18 ± 1.8 min in the 1% ropivacaine group and after 27 ± 2.3 min in the 0.5% group.

INTENSITY OF MUSCLE BLOCKADE. Maximal intensity of motor blockade was registered at 90 min for 1% ropivacaine, whereas it took 60 min for the 0.75% and 0.5% solutions. Muscles involved in knee extension were most blocked, followed first by muscles of hip

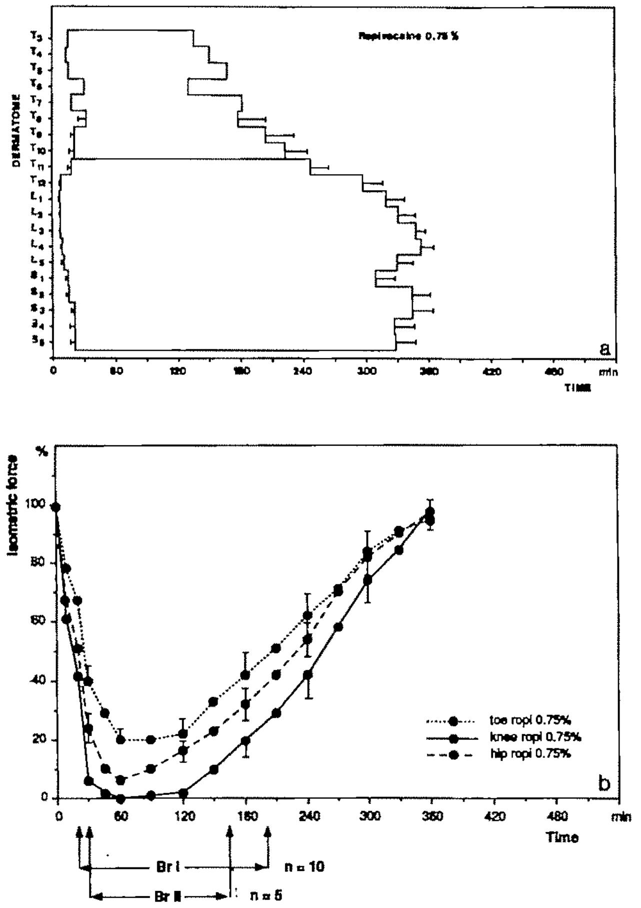


Figure 3. Onset, duration, and regression of sensory (a) and motor (b) epidural blockade with 0.75% ropivacaine in 10 volunteers (mean ± SEM). Toe flexion was significantly slower in onset than hip flexion and knee extension ($P < 0.05$).

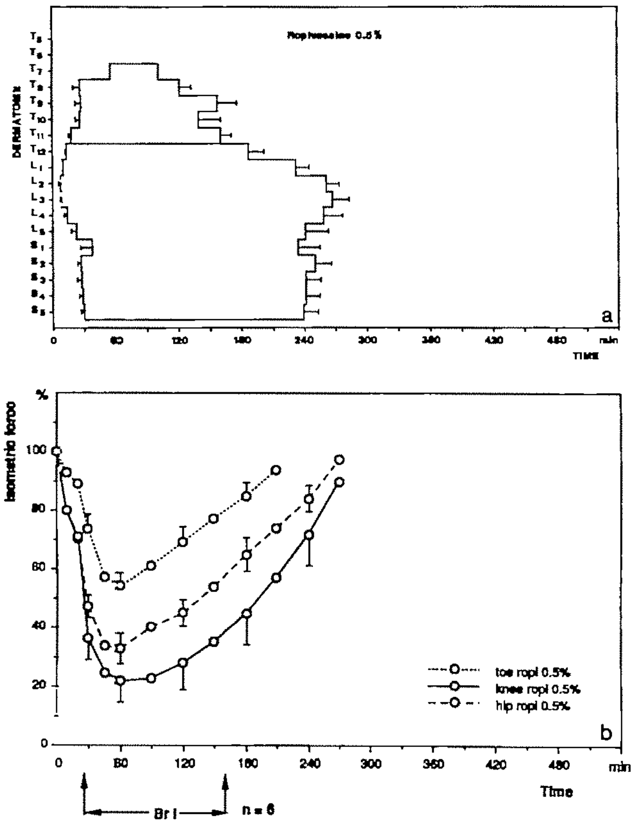


Figure 4. Onset, duration, and regression of sensory (a) and motor (b) epidural blockade with 0.5% ropivacaine (mean ± SEM). Toe flexion was significantly slower in onset, whereas knee extension was slowest in regression ($P < 0.05$).

flexion and then by those of toe flexion, regardless of concentration used (Figures 2b, 3b, and 4b). Motor blockade with 1% ropivacaine was profound for all three movements: at 90 min 0% of muscle force was present for knee extension, 1% for hip flexion, and 6% for toe flexion. Comparing the groups, 1% and 0.75% ropivacaine caused a more intense blockade, and 0.5% ropivacaine caused a significantly more superficial blockade, regardless of the type of movement.

Duration of maximal motor blockade was longest for knee extension in the 1% ropivacaine group (258 min). There were no significant differences between movements in the other groups. Regardless of the type of movement, the longest maximal blockade was encountered in the 1% ropivacaine group; there were no significant differences in the duration of maximal motor blockade between the 0.75% and 0.5% solutions.

REGRESSION. Regression of muscle blockade in the 1% and 0.75% groups was similar for all three movements (Figures 2b and 3b). With 0.5% ropivacaine, the muscle strength for knee extension was slowest to return to baseline throughout the regression (Figure 4b).

The time from epidural injection to 90% recovery of muscle strength for all movements was longest with 1% ropivacaine (448 ± 18.2 min). There were no significant differences between the 0.75% and 0.5% solutions in this respect (320 ± 13.5 and 254 ± 28.7 min; Table 2).

Relationship Between Sensory and Motor Blockade

In the 1% ropivacaine group almost total muscle paralysis was present for all movements (0%–6% of baseline muscle force), whereas only three subjects had Bromage grade 3 (Figure 2b). However, there were two more subjects with unilateral grade 3 block. In all the ropivacaine groups, the Bromage score returned to 0 during the regression phase significantly earlier for all movements than regression to 90% of the isometric force. The only exception was

Table 2. Recovery of Pinprick Perception and of Motor Strength Evaluated by the Bromage Scale and Measured by the Quantitative Method Described in the Text

	Ropivacaine					
Complete recovery of:	1%		0.75%		0.5%	
Sensory blockade	411 ± 17.2	[a]	353 ± 11.9	[a]	268 ± 14.7	[a]
Bromage 1 to 0	298 ± 10.7	[b]	199 ± 15.4	[b]	160 ± 21.3	[b]
Isometric motor force (knee extension)	448 ± 18.2		320 ± 13.5		254 ± 28.7	

Values are expressed as mean ± SEM.

[a] Significant differences in time to recovery for pinprick perception versus Bromage score change from 1 to 0.

[b] Significant differences in time to recovery for 90% of isometric muscle force versus Bromage score change from 1 to 0.

toe flexion in the 0.5% group. At the change of Bromage score from grade 1 to 0, only 22%–40% of the muscle force for knee extension (assessed by the quantitative method) had recovered (Figures 2b, 3b, and 4b). From that point (Bromage score just changed to 0) 1.5–2.5 h passed before all movements had returned to 90% of baseline force and the subjects could be mobilized.

The Bromage score changed from grade 1 to 0 1.7–2.6 h before complete recovery of sensation (a significant difference for all groups—Table 2). Recovery of analgesia and return to 90% of baseline isometric muscle force were both related to time, but there was a tendency for sensory blockade to outlast motor blockade in the 0.75% and 0.5% groups. Complete recovery from motor blockade occurred significantly earlier than did recovery of pinprick sensation for the muscles of hip and toe flexion in the 0.5% group. This was also the case when sensory segments corresponding to motor innervation (L1-3 and L5-S2) were taken into consideration ($P < 0.05$).

Mobilization

After regression of muscle paralysis to 90% of baseline strength for all movements was registered, the subject was mobilized. The time from epidural injection to mobilization was longest in the volunteers given 1% ropivacaine (494 ± 16 min), followed by those in the 0.75% group (390 ± 12 min), and then by the 0.5% group (320 ± 22 min)—significant differences between all three groups.

In two cases, extensive residual analgesia was present at the time of mobilization. In subject 1, patchy analgesia was present from L-2 downward; in subject 2, it reached from T-12 to S-5 (both received 0.75% ropivacaine). Both were carefully mobilized. There were no problems in doing so in subject 1, but when subject 2 stood up from the sitting position, he reacted with tachycardia and hypotension (pulse increased from 96 to 118, systolic blood pressure decreased from 132 to 88 mm Hg). He was otherwise remarkably unaffected, and pulse and blood pressure recovered rapidly and spontaneously. He could support himself in the standing position but was clearly ataxic and unstable when trying to walk. He returned to the supine position for the next 1.5 h while sensory analgesia disappeared and was then mobilized without further problems.

Six of the 30 subjects had unstable stance because of a "cushiony" feeling in their feet (four in the 0.75% group and one each in the 1% and 0.5% groups). Eight subjects felt unstable in their knees while jogging (three in the 0.5% and 1% groups and two in the 0.75% group). These residual disturbances disappeared 45–60 min after mobilization.

Urinary Bladder

The time from epidural injection to spontaneous urination was longest for the 1% ropivacaine group (559 ± 12 min), 442 ± 11 min for 0.75% ropivacaine, and 349 ± 13 min for 0.5% ropivacaine. Three subjects who received the 1% solution were catheterized during the investigation because of bladder distention. The average time between mobilization and spontaneous micturition was 30–50 min.

Circulation

All but one of our subjects showed hemodynamic stability throughout the investigation. This subject, who was receiving 0.75% ropivacaine, reacted with a more than 30% decrease below baseline levels with bradycardia at the point of maximal epidural spread (90 min after epidural injection). He recovered promptly after atropine and ephedrine intravenous injection. Two persons had short periods of tachycardia and paleness during mobilization without blood pressure variations.

Discussion

Our subjects consisted of 30 well-trained male volunteers in each of whom epidural blockade was established. The subjects were hemodynamically stable throughout the procedure, and only one experienced a short hypotension. No inadvertent effects were registered.

In this study, 1%, 0.75%, and 0.5% ropivacaine showed the same ability to block pain perception without missing segments. Sensory blockade was well established in the lower lumbar and sacral segments, segments notoriously difficult to block during epidural anesthesia. Ropivacaine should, therefore, be a potentially useful anesthetic in orthopedic surgery. As with other local anesthetics (8), the spread of analgesia did not increase with increase in ropivacaine dose. An increase in dose from 100 to 200 mg ropivacaine prolonged the duration of analgesia, which is also in agreement with other studies (3).

As regards motor blockade, the results of our study indicate dose dependency. Onset was quicker, intensity greater, regression slower, and duration longer with increasing concentrations. Motor blockade was also dose dependent when measured by the Bromage scale, which is in agreement with the findings of other investigators (3,9). The grading of intensity by Bromage scale is, however, not precise. Only three subjects (and two with unilateral block) in the 1% ropivacaine group had Bromage grade 3 block, while their isometric muscle force measured by the quantitative method was less than 10% of the baseline strength. In the regression phase only 30%–40% of baseline muscle strength was present in the 1% and 0.75% ropivacaine groups at the time when the Bromage scale indicated no motor blockade (Bromage score = 0). This difference in precision between the two methods explains why motor recovery judged by the Bromage scale was encountered 1.5–2.5 h before sensory recovery, while quantitatively assessed muscle force returned to baseline strength simultaneously with recovery of pain perception.

Plantar flexion of the big toe (L5-S2) was more difficult to block than were other movements, with higher innervation levels (L1-4), even with high doses. This phenomenon has also been described with bupivacaine, mepivacaine, and etidocaine (7). One possible explanation for this is the larger diameters of L5-S2 spinal roots, which are more difficult to anesthetize (10). Another explanation could be that with the increase in distance from the injection site (L2-3), the amount of local anesthetic available decreases. This would result in slower onset and less profound motor blockade of L5-S2 segments, which was the case in our study. Recovery of muscle strength to 90% of the baseline value came significantly earlier than recovery of pain perception only in the 0.5% ropivacaine group and for the muscles of toe and hip flexion. The reason for this might be that higher doses of ropivacaine anesthetize large motor neurons to the same degree as smaller sensory ones. The differential block (i.e., sensory fibers affected more than motor) was encountered when a low dose/concentration of ropivacaine was used. It is not surprising that muscles of knee extension in the 0.5% group behaved differently, as their innervation level lies closest to the injection site so that they received a large amount of ropivacaine. Our results, which are supported by others (3), demonstrate a local anesthetic profile, motor versus sensory fiber blockade, similar to that which has been found with epidural bupivacaine (11).

Comparisons of 20 mL of 0.5% bupivacaine and 0.5% ropivacaine for epidural use in patients scheduled for orthopedic surgery found the two drugs to be clinically equieffective (12). There were no differences in the spread of sensory blockade. Duration of analgesia and intensity of motor blockade were slightly longer and deeper with bupivacaine. Another investigation also reported that 0.5% ropivacaine for epidural use is very similar to 0.5% bupivacaine (1). On referring to an earlier study by us, with the same methods and on comparable material as in this investigation (7), the duration of analgesia for 0.5% ropivacaine is seen to lie between those for 2% mepivacaine and 0.5% bupivacaine (both with adrenaline), whereas that for 0.75% ropivacaine resembles that for 0.5% bupivacaine with adrenaline. In contrast to bupivacaine, which failed to block L5-S1 segments in 3 of 10 subjects, ropivacaine caused loss of pinprick perception in this area in all subjects. As for motor blockade, 0.75% ropivacaine was comparable to 0.5% bupivacaine, but maximal motor blockade with bupivacaine lasted longer. This could be the result of added adrenaline.

It is interesting to note that pinprick perception returned at the same time that isometric muscle power regressed to 90% of baseline strength, even though there was a tendency for sensory blockade to outlast motor blockade, as shown by the two subjects who had pronounced analgesia while mobilized.

In conclusion, ropivacaine has good analgetic properties in all three concentrations used in this study. Ropivacaine 1% causes profound motor block, but motor blockade is more modest with the 0.5% solution. The average total duration of sensory and motor blockades (assessed by quantitative method) was 7.5, 6, and 4.5 h (5:4:3) for ropivacaine 1.0%, 0.75%, and 0.5%, respectively. These qualities ensure wide clinical application possibilities: from obstetric cases and outpatient and pain clinics using 0.5% ropivacaine, to long orthopedic operations requiring good muscle relaxation with 1% ropivacaine.

The help and guidance of Bertil Löfström, Professor emeritus of Anesthesiology, Linköping University, is greatly appreciated. The assistance of Ing-Marie Dimgren is gratefully acknowledged.

References

1. Bannister J, Clark C, Littlewood DG. Ropivacaine: a preliminary clinical trial. Br J Anaesth 1989;63:237P.
2. Katz JA, Bridenbaugh PO, Knarr DC, Helton SH, Denson DD. Pharmacodynamics and pharmacokinetics of epidural ropivacaine in humans. Anesth Analg 1990;70:16–21.
3. Concepcion M, Arthur GR, Steele SM, Bader AM, Covino BG. A new local anesthetic, ropivacaine. Its epidural effects in humans. Anesth Analg 1990;70:80–5.
4. Lanz E, Theiss D, Kellner G, Zimmer M, Staudte H-W. Assessment of motor blockade during epidural anesthesia. Anesth Analg 1983;62:889–93.
5. Axelsson K, Widman GB. A comparison of bupivacaine and tetracaine in spinal anaesthesia with special reference to motor block. Acta Anaesthesiol Scand 1985;29:79–86.
6. Axelsson K, Hallgren S, Widman B, Olstrin P-O. A new method for measuring motor block in the lower extremities. Acta Anaesthesiol Scand 1985;29:72–8.
7. Axelsson K, Nydahl P-A, Philipson L, Larsson P. Motor blockade after epidural injection of mepivacaine, bupivacaine and etidocaine. A double-blind study. Anesth Analg 1989;69:739–47.
8. Scott DB, McClive JH, Giasi RM, Seo J, Covino BG. Effects of concentrations of local anaesthetic drugs in extradural block. Br J Anaesth 1980;52:1033–7.
9. Niesel HC, Eilingsfeld T, Kaiser H, Klimpel L. Ropivacain zur Periduralanaesthesie. Untersuchungen zur Dosis-Wirkungsrelation bei orthopädischen Eingriffen. Reg Anaesth 1990;13:73–7.
10. Galindo J, Hernandez J, Benavides O, Ortegon de Munoz S, Bonica JJ. Quality of spinal extradural anaesthesia: Influence of spinal nerve root diameter. Br J Anaesth 1975;47:41–6.
11. Bromage PR. Epidural analgesia. 1st ed. Philadelphia: WB Saunders, 1978:458–60.
12. Carpenter RL, Brown DL, Thompson GE. Ropivacaine vs bupivacaine: a randomized, double-blind, comparison for epidural anesthesia. Anesth Analg 1990;70:S49.

Continuous Infusion of Interpleural Bupivacaine Maintains Effective Analgesia After Cholecystectomy

Charles E. Laurito, MD, Louise I. Kirz, MD, Timothy R. VadeBoncouer, MD, Francis X. Riegler, MD, Gregg M. Citron, MD, Laurence J. Segil, MD, and Dale A. Pelligrino, PhD

LAURITO CE, KIRZ LI, VADEBONCOUER TR, RIEGLER FX, CITRON GM, SEGIL LJ, PELLIGRINO DA. Continuous infusion of interpleural bupivacaine maintains effective analgesia after cholecystectomy. Anesth Analg 1991;72:516–21.

Twenty-five patients who had undergone elective cholecystectomy were prospectively randomized to receive via an interpleural catheter either a continuous infusion of 0.25% bupivacaine at 0.125 $mL \cdot kg^{-1} \cdot h^{-1}$ ($n = 13$) or repeated bolus injections ($n = 12$) of 0.5% bupivacaine with epinephrine 1:200,000 at 0.4 mL/kg every sixth hour. Adequacy of pain relief was measured by the amount of patient-controlled analgesia morphine required postoperatively and by patient scores on a visual analog scale obtained every sixth hour. Two venous blood samples for measurements of serum bupivacaine levels were obtained from patients in the continuous group at hours 6 and 24; four blood samples were obtained from patients in the bolus group, both immediately before and 30 min after injections at hours 6 and 24. Among the patients receiving the bolus injections, morphine was required 62 ± 15 (SEM) times over the 24-h study period with total morphine dosage averaging 30 ± 15 mg. Corresponding values for patients in the continuous group were 35 ± 10 times and 23 ± 5 mg of morphine. The difference was not, however, statistically significant, but when activity during the 2-h time periods immediately before reinjection were examined, patients in the bolus group required and received significantly more morphine than did those in the continuous group ($P < 0.05$). Patients in the continuous group had visual analog scale scores that averaged 2.9 ± 0.6 over the 24-h study period. Patients within the bolus group had visual analog scale scores before and again 30 min after injection that averaged 5.8 ± 0.8 and 1.8 ± 0.5, respectively ($P < 0.05$). Serum bupivacaine levels increased in both groups between the sixth and 24th hour measurements; the average postinjection bupivacaine levels were significantly higher ($P < 0.05$) with intermittent injection than corresponding levels in the continuous infusion group. The bupivacaine level rose to 3.2 ± 0.4 μg/mL 30 min after the bolus injection at hour 24. In summary, continuous interpleural infusion of 0.25% bupivacaine provides safer and more effective postoperative pain relief after cholecystectomy than does intermittent interpleural injection of 0.5% bupivacaine with epinephrine every 6 h.

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHETIC TECHNIQUES, REGIONAL—interpleural local anesthetics. PAIN, POSTOPERATIVE.

Several investigators have reported successful pain relief after cholecystectomy with the use of bolus injections of bupivacaine through an interpleural catheter (IPC) (1–4). In these reports, the catheter usually is placed interpleurally at the conclusion of the operation; local anesthetic is injected and the general anesthetic then discontinued. The catheter is subsequently reinjected with bupivacaine as needed to maintain adequate analgesia. The frequency of reinjection is determined by the patient's perception of pain. This interval varies among patients and can be as frequent as every 3 h when a patient-controlled analgesia (PCA) device is used to monitor narcotic demand (5).

Although the catheter technique provides an elegant, site-specific method for pain relief, it can be very labor-intensive to maintain. A physician must be available 24 h a day to assess the patient's degree of pain, repeat the injection, and watch for signs of toxicity. Because the manpower requirements are so

---

Received from the Departments of Anesthesiology, University of Illinois at Chicago and Michael Reese Hospital, Chicago, Illinois; Harvard University, Cambridge and Brigham and Women's Hospital, Boston, Massachusetts; and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Accepted for publication November 23, 1990.

Address correspondence to Dr. Laurito, Michael Reese Hospital and Medical Center, Lake Shore Drive at 31st Street, Chicago, IL 60616.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

large, some departments may find it impossible to offer this form of pain relief to patients. We hypothesized that a continuous infusion of bupivacaine into the interpleural space might provide sustained pain relief and thereby limit the systemic narcotic requirements that are needed when repeated interpleural bolus injections of bupivacaine are used. Furthermore, such a technique might avoid the large peaks in serum bupivacaine levels seen with repeat interpleural bolus injections and possibly provide a more stable degree of analgesia.

Methods

After approval by our institutional review board, 25 ASA physical status I and II patients scheduled to undergo cholecystectomy gave written consent to participate in the study. All patients underwent general anesthesia with an inhalational agent and had no pre- or intraoperative narcotic except for 100 μg fentanyl toward the conclusion of the operation. At this time, the effects of muscle relaxation were reversed and the patient was allowed to breathe spontaneously while the IPC was placed. We chose the anterior axillary line just superior to the sixth rib as our entry site. After the area was aseptically cleansed and draped, an 18-gauge modified Hustead needle was advanced at a 90° angle to the skin. The stylet was removed and a glass syringe filled with 2 mL bupivacaine and 2 mL air was attached to the needle and advanced until the parietal pleura was perforated and the plunger pulled inward. The bevel of the needle was directed toward the patient's right shoulder, and an epidural catheter was threaded 5 cm through it. The needle was then withdrawn and the catheter secured with a sterile dressing. Before awakening and extubation, each patient received 0.4 mL/kg of 0.5% bupivacaine with epinephrine 1:200,000 with a dose not in excess of 35 mL. Chest x-rays were not obtained after IPC placement. Careful note was made of the patient's breath sounds, respiratory rate, tidal volume, and oxygen saturation as measured by pulse oximetry before and after insertion of the needle and catheter. No changes suggestive of a pneumothorax occurred.

Patients had been randomized preoperatively to receive either a continuous infusion of plain 0.25% bupivacaine at 0.125 $\mathrm{mL \cdot kg^{-1} \cdot h^{-1}}$ (12 patients) or repeat bolus injections of 0.5% bupivacaine with epinephrine at 0.4 mL/kg every sixth hour (13 patients). Because of the equipment required for infusion of medication, it was impossible to double-blind the study. The infusion rate used was chosen because during a 6-h time period it provides approximately the same amount of local anesthetic as is delivered by repeated bolus injections. Epinephrine was not thought to be needed to slow systemic absorption in the continuous group because of the relatively slow rate of infusion compared with bolus injection. Patients who received bolus injections were kept supine during the IPC injections and for 20 min thereafter. No position constraints were placed on those receiving continuous infusions; they were encouraged to sit and even to ambulate during the infusion. Patients in both groups had been previously oriented to the use of PCA equipment (Abbott Lifecare PCA infuser 4100). This was made immediately available to them as they entered the postanesthetic care unit. Morphine sulfate dosages were set at bolus 0, continuous 0, PCA 1 mg with a lockout period of 5 min. Patients were encouraged to use PCA as needed to provide relief from abdominal pain.

Patients in the continuous infusion group had venous blood samples for measurement of serum bupivacaine levels drawn at hours 6 and 24 (a gas chromatographic procedure following the method of Park et al. [6] performed by National Medical Services, Willow Grove, Pa.). In addition, visual analog scale (VAS) pain scores were obtained every 6 h. Patients in the bolus group had IPC injections every 6 h. Blood samples were drawn immediately before and 30 min after the injections at hours 6 and 24. Visual analog scale scores were also obtained every 6 h both before and 30 min after each injection throughout the night. Twenty-four-hour PCA-usage logs were printed from all PCA devices to document the number of demands for morphine sulfate made, and the amount of narcotic the patient actually received.

Statistical significance was evaluated by two-way analysis of variance for repeated measures, the Tukey–Kramer post hoc test, and the unpaired Student's *t*-test. A *P* value less than 0.05 was considered to be statistically significant. A Bonferroni correction for multiple comparisons was made when appropriate. Data are expressed as mean ± standard error of the mean.

Results

Patients in each group were similar with respect to age, sex, weight, and ASA classification (Table 1). All had subcostal incisions for cholecystectomy without common bile duct exploration or additional incidental procedure. No patient suffered a complication from catheter insertion, drug injection, or drug infusion.

Table 1. Characteristics of Patients Assigned to Treatment Groups

Treatment	*n*	Age (yr)	Sex (M/F)	Weight (kg)	ASA status (I/II)
Continuous infusion	13	42 ± 13.5	2/11	77.9 ± 13	10/3
Intermittent injections	12	39.7 ± 13.7	1/11	77.2 ± 22	8/4

Values for age and weight are expressed as mean ± SD.
No significant differences among treatment groups for any variable.

Among the patients receiving bolus injections of bupivacaine, demand for morphine sulfate was made an average of 62 ± 15 times; morphine sulfate given averaged 30 ± 15 mg during the 24-h study period. These patients demanded and received significantly more morphine sulfate during the 2-h intervals before repeat injections than did patients in the continuous infusion group during these same time intervals (see Figure 1). Among the patients receiving continuous infusions, cumulative demand for and receipt of morphine sulfate averaged 35 ± 10 times and 23 ± 5 mg during the study period; these differences tended toward, but did not achieve, significance (*P* = 0.12 and 0.17, respectively).

In the continuous infusion group, VAS scores averaged 2.9 ± 0.6 over the 24-h study period. In patients in the bolus group, VAS scores before and 30 min after IPC injection averaged 5.8 ± 0.8 and 1.8 ± 0.5, respectively. The preinjection VAS scores in the bolus group were significantly higher than both the postinjection and continuous infusion VAS scores (see Figure 2).

Serum bupivacaine levels increased in both groups between hours 6 and 24 (Figure 3). In the continuous infusion group, the average 6-h plasma level of 1.2 ± 0.1 μg/mL increased to 1.8 ± 0.2 μg/mL at hour 24. Within the bolus group, the 6-h preinjection average of 0.7 ± 0.1 μg/mL increased to 1.9 ± 0.2 μg/mL 30 min after injection. At hour 24, the preinjection level of 1.8 ± 0.2 μg/mL climbed to 3.2 ± 0.4 μg/mL 30 min after reinjection. In the bolus group, average postinjection bupivacaine levels were significantly higher than corresponding bupivacaine levels in the group receiving a continuous infusion.

Discussion

Interpleural injections of bupivacaine have been shown to be safe in the treatment of postcholecystectomy pain (1,2,5). Analgesia is localized to the surgical site, and the need for supplemental narcotics is diminished (5). The initial reports of prolonged pain relief, however, have not been supported by subsequent studies. Many investigators have shown only 3–4 h of analgesia despite the use of larger bolus doses of bupivacaine than initially described (5,7,8). Our experience confirms these findings. Because of the need for frequent reinjections, the IPC technique is much less attractive than the initial report of its use suggested. The demand on an anesthesiologist's time can be so prohibitive that departments may not be able to offer the technique. We hypothesized that a continuous infusion of IPC bupivacaine might provide analgesia that is at least as satisfactory as that achieved by intermittent bolus injections while avoiding wide swings in plasma bupivacaine levels.

Our findings indicate that the continuous infusion method of bupivacaine delivery is superior to that of repeat bolus injections. When the degree of pain a patient experiences was assessed by VAS, patients in the bolus group complained of significantly more pain immediately before each of the four reinjections than 30 min after the injection. They also had significantly more pain than did patients having a continuous interpleural infusion of bupivacaine at a comparable time. This is further evidenced when the demand for morphine sulfate and amount given, as recorded from PCA infusion devices, is used as an index of the amount of pain a patient had. During each of the 2-h intervals before reinjection, patients in the bolus group demanded and received significantly more morphine sulfate than did those in the continuous infusion group. During the 24-h study period, patients in the bolus group needed more morphine sulfate than did those in the continuous group. This difference, however, did not achieve statistical significance.

When blood levels are examined, the superiority of the infusion method is even clearer. Patients having bolus interpleural injections had serum levels that significantly increased 30 min after each injection. When hour-6 levels are examined, patients in the bolus group had levels that were both significantly higher than those of patients in the continuous group and also close to a toxic level. At hour 24, the preinjection serum bupivacaine levels were comparable to levels in the continuous infusion group. Thirty minutes after bupivacaine injection, however, serum levels increased significantly so that 6 of the 12 patients had levels well within the toxic range (Figure 4). One patient had a level of 4.7 μg/mL. No signs or symptoms of toxicity were noted by the examiner who was present to obtain a repeat VAS score and blood sample. These high levels are troubling and call

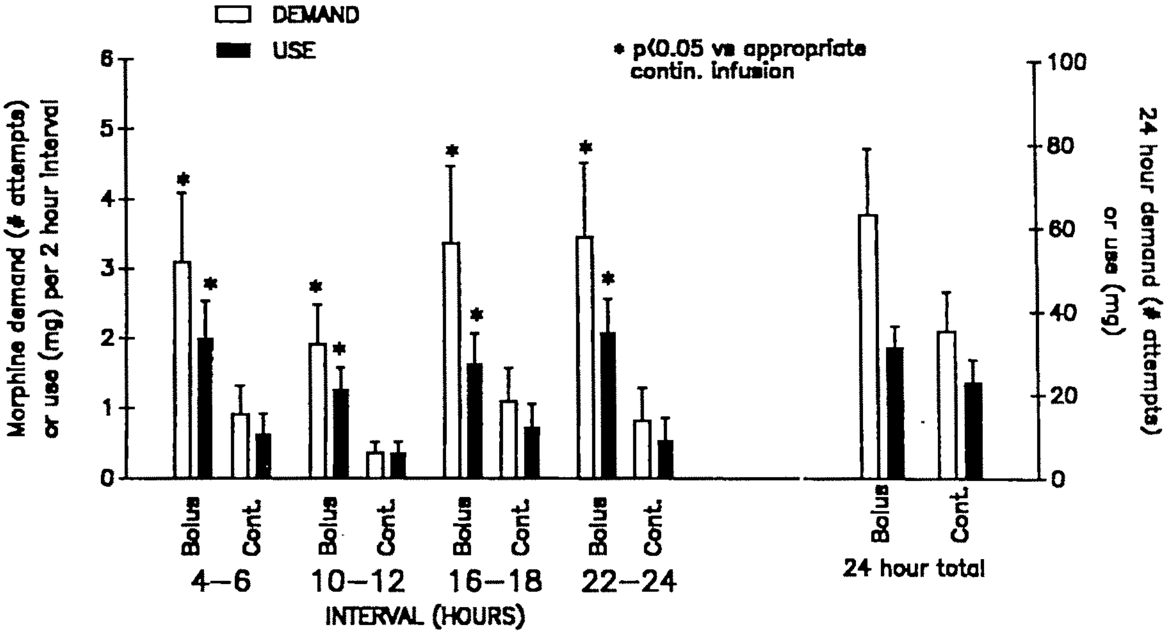


Figure 1. Morphine demand and use during four 2-h intervals and over the entire 24 h of study in patients having either continuous interpleural infusion or repeat interpleural injections (every 6 h) of bupivacaine. Results are expressed as mean ± SE.

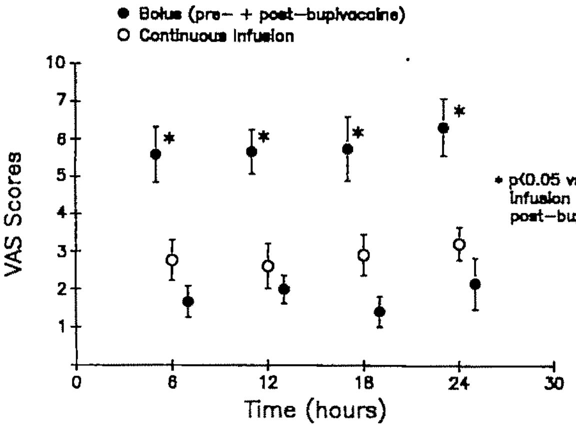


Figure 2. Visual analog pain scale scores in patients having a continuous interpleural infusion or bolus injections of bupivacaine. Scores in the latter group were made before and after each injection. Values are expressed as mean ± SE.

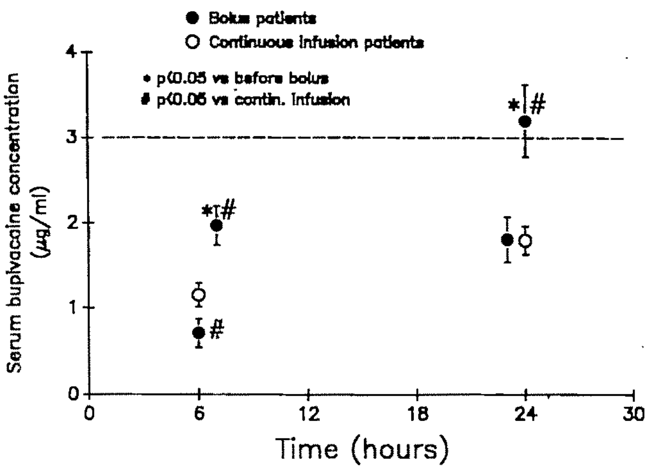


Figure 3. Serum bupivacaine concentrations in the patient groups represented in the previous two figures. Samples for analysis in patients having repeated interpleural injections were obtained before and after bupivacaine injections at 6 and 24 h. Single samples were obtained at 6 and 24 h in the continuous infusion group. Values are expressed as mean ± SE.

into question the safety of prolonged use of this technique. Even patients in the continuous infusion group showed a trend toward toxicity when the 24-h levels are compared with those from hour 6.

Several other investigators have used continuous interpleural infusions of bupivacaine. Rocco et al. used the technique in treating three patients with multiple, traumatic rib fractures (9). All patients were initially given 20 mL of 0.5% bupivacaine, after which they received a continuous infusion of 0.25% or 0.5% bupivacaine at 5–10 mL/h for 5–10 days. The 0.5% concentration provided excellent pain relief with a venous bupivacaine level ranging from 1.1 to 2.4 µg/mL measured only at 1 and 6 h after onset of the infusion. No signs of toxicity were reported.

McIlvaine et al. studied children after thoracotomy (10). When the patient was alert in the postanesthetic care unit, a continuous infusion of 0.25% bupivacaine with 1:200,000 epinephrine was begun at a rate of 0.5 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$. If analgesia was inadequate as

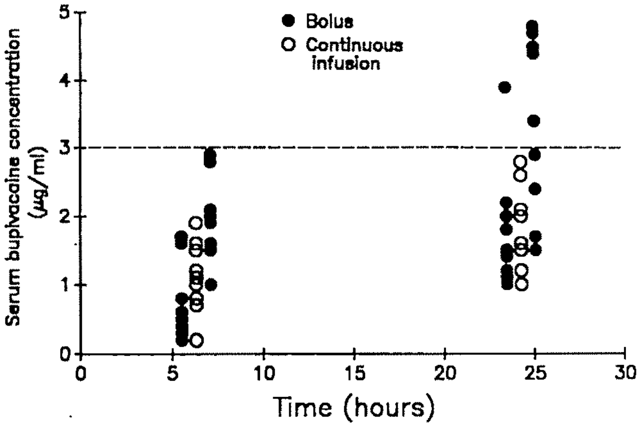


Figure 4. Individual values for the results summarized in Figure 3. The *dashed line* represents the reported serum concentration threshold for the appearance of symptoms of toxicity.

assessed by the patient's nurse, the infusion was increased up to 1 $mL \cdot kg^{-1} \cdot h^{-1}$. Narcotic was given only if pain persisted while the patient received the maximum rate of bupivacaine infusion for 30 min. Narcotics were not required by any patient during the infusion. Arterial bupivacaine concentrations were measured every 4 h. In their 14 patients, 11 attained plasma bupivacaine levels >2 μg/mL, five patients >4 μg/mL, and one patient >7 μg/mL during 24 h of therapy. No patient had signs or symptoms of cardiovascular or central nervous system toxicity.

Rosenberg et al. also examined the use of continuous IPC infusions of bupivacaine in 14 adults who had undergone thoracotomy (11). Results were less favorable in that all patients complained of chest pain and had to be medicated with intramuscular narcotics. They found that IPC bupivacaine administration was unsatisfactory in the management of postthoracotomy pain and theorized that there was inadequate delivery of the medication to the target nerves because of chest tube drainage. At hour 24, mean plasma bupivacaine levels averaged 1.6 ± 1.0 μg/mL with one individual reaching 3.68 μg/mL. Again, no signs of toxicity were noted.

Our study differs from others in that we randomly assigned patients to receive either continuous or bolus IPC bupivacaine after cholecystectomy. Our patients all had immediate access to systemic morphine sulfate via PCA equipment and were encouraged to use the narcotic to relieve any right upper quadrant pain. We assessed their degree of discomfort by the use of VAS scores obtained every 6 h as well as by the examination of morphine sulfate demand/receipt logs from the PCA machines. Serum levels were measured at specific times during the 24-h study period to determine bupivacaine levels.

We found no complications associated with the use of either technique. After a brief explanation, the nursing staff was able to care for the patients with the continuous infusions with little additional input from our department. We were available every 6 h to obtain blood samples and VAS scores, yet found that we had to expend no additional effort for the care of these patients. Use of this technique without such attentiveness from the anesthesia staff will be needed to determine if a continuous infusion truly allows for decreased physician input.

The high serum bupivacaine levels were surprising especially in light of this ASA I and II patient population with no liver or kidney impairment. The trend toward toxicity suggests that prolonged use of this technique should take place only with concurrent measurements of serum bupivacaine levels. No signs of toxicity were noted despite levels much higher than the 2–4-μg/mL range described as causing central nervous system changes. This is in keeping with other reports of high bupivacaine levels with no symptoms and confirms work by Scott that the absolute toxic plasma concentration is more dependent on the rate of change in the plasma than on any specific concentration (12).

In summary, the use of a continuous IPC infusion of 0.25% plain bupivacaine for postcholecystectomy patients provided safer and more effective pain relief than is provided by injections every sixth hour. Patients requested and received morphine sulfate less frequently than did those given interpleural injections every 6 h. This difference tended toward but did not achieve significance. When the 2-h periods before each repeat injection were examined, patients in the continuous infusion group had significantly less pain than did those having bolus injections. This was measured both by lower VAS scores and by decreased demand and receipt of morphine sulfate. Patients in the continuous infusion group had lower serum bupivacaine levels, although some patients in both groups had increases in bupivacaine levels over the 24-h study period. No complications were noted in patients in either group.

References

1. Reiestad F, Stromskag FE. Interpleural catheter in the management of postoperative pain. Reg Anesth 1986;11:89–91.
2. Scott NB, Mogensen T, Bigler T, Kehlet H. Comparison of the effects of continuous interpleural vs epidural administration of 0.5% bupivacaine on pain, metabolic response and pulmonary function after cholecystectomy. Acta Anaesthesiol Scand 1989; 33:535–9.
3. Bruce DL, Gerken MV, Lyon GD. Postcholecystectomy pain

relief by interpleural bupivacaine in patients with cystic fibrosis. Anesth Analg 1987;66:1187–9.

4. Frank ED, McKay W, Rocco A, Gallo JP. Interpleural bupivacaine for postoperative analgesia following cholecystectomy: a randomized prospective study. Reg Anesth 1990;15:26–30.
5. VadeBoncouer TR, Riegler FX, Gautt RS, Weinberg GL. A randomized, double-blind comparison of the effects of interpleural bupivacaine and saline on morphine requirements and pulmonary function after cholecystectomy. Anesthesiology 1989;71:339–43.
6. Park GB, Erdtmansky PE, Brown RR, Kullberg MP, Edelson J. Analysis of mepivacaine, bupivacaine, etidocaine, lidocaine, and tetracaine. J Pharm Sci 1980;69:603–5.
7. Seltzer JL, Larijani GE, Goldberg ME, Marr AT. Interpleural bupivacaine—a kinetic and dynamic evaluation. Anesthesiology 1987;67:798–800.
8. Strömskag KE, Reiestad F, Holmqvist ELO. Intrapleural administration of 0.25%, 0.375%, and 0.5% bupivacaine with epinephrine after cholecystectomy. Anesth Analg 1988;67: 430–4.
9. Rocco A, Reiestad F, Gudman J, McKay W. Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures. Reg Anesth 1987;12:10–4.
10. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via interpleural catheter for analgesia after thoracotomy in children. Anesthesiology 1988; 69:261–4.
11. Rosenberg PH, Scheinin BM, Scheinin A, Lepäntalo MJA, Lindford O. Continuous interpleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology 1987;67:811–3.
12. Scott DB. Evaluation of clinical tolerance of local anaesthetic agents. Br J Anaesth 1975;47:328.

Comparison of Epidurally Administered Sufentanil, Morphine, and Sufentanil-Morphine Combination for Postoperative Analgesia

Raymond S. Sinatra, MD, PhD, Ferne B. Sevarino, MD, James H. Chung, MD,
George Graf, MD, Darcy Paige, RN, Victor Takla, MD, and David G. Silverman, MD

SINATRA RS, SEVARINO FB, CHUNG JH, GRAF G, PAIGE D, TAKLA V, SILVERMAN DG. Comparison of epidurally administered sufentanil, morphine, and sufentanil-morphine combination for postoperative analgesia. Anesth Analg 1991;72:522–7.

Postoperative analgesia provided by epidurally administered sufentanil and/or morphine was evaluated in 45 patients recovering from major gynecologic surgery. At the first complaint of pain in the Postanesthesia Care Unit, patients received a single epidural bolus of 30 μg sufentanil (group A), 5 mg morphine (group B), or 30 μg sufentanil plus 3 mg morphine (group C) in a randomized blinded fashion. Analgesic efficacy was assessed throughout the 24-h study period with 10-cm visual analog scales. The need for additional postoperative analgesia (patient-controlled analgesia, 1 mg of morphine every 6 min as necessary) and the incidence of adverse effects were also assessed.

Patients receiving sufentanil (groups A and C) had significantly faster onset of analgesia than did patients given morphine alone (group B, $P < 0.05$). Group B subjects experienced the longest duration of analgesia (B vs A and C, $P < 0.05$) and required significantly less patient-controlled analgesia (morphine) than patients in group A ($P < 0.05$). No patient developed clinically significant respiratory depression or excessive sedation, and there were no intergroup differences in incidence of pruritus or nausea (P value not significant). The data indicate that a mixture of sufentanil and morphine provides either a more rapid onset of epidural analgesia or reduced patient-controlled analgesia narcotic requirement than respective doses of each agent administered alone.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—opioids. PAIN, POSTOPERATIVE. ANALGESICS, MORPHINE, SUFENTANIL.

Preservative-free preparations of morphine provide effective and prolonged epidural analgesia and are commonly administered after a variety of surgical procedures (1–3). Morphine's low lipid solubility and its propensity to remain sequestered in cerebrospinal fluid (4) are responsible for a number of less desirable characteristics, including a delayed onset of peak analgesic effect (5) and late-onset respiratory depression (6,7). Although highly lipophilic opioids such as sufentanil provide a more rapid onset of pain relief (8–10), duration of epidural analgesia is limited (9–11) unless the drug is continuously infused (12).

The combination of morphine and a more lipophilic opioid has been advocated as a method to improve the overall quality of epidural analgesia; however, research in this area has yielded conflicting results. Although preliminary evaluations found more rapid onset and an additive duration of pain relief (11,13,14), a recent investigation (15) reported that the combination of morphine and fentanyl provided less effective postoperative analgesia than morphine alone.

The following randomized double-blind investigation examined the safety and efficacy of postoperative analgesia provided by a mixture of sufentanil, a lipophilic opioid having high affinity for spinal cord μ-receptors, and preservative-free morphine.

Materials and Methods

The present investigation was approved by the Yale University School of Medicine Human Investigations Committee and required informed written consent. Healthy women (ASA physical status I and II) presenting for elective abdominal hysterectomy and requesting both epidural anesthesia and postoperative intravenous patient-controlled analgesia (PCA) were

---

Received from the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication November 23, 1990.

Address correspondence to Dr. Sinatra, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, Box 3333, New Haven, CT 06510.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

invited to participate. Exclusion criteria included age over 65 yr, weight over 100 kg, history of alcohol or opioid abuse, and allergy to morphine or sufentanil. Patients were instructed in the use of the PCA device and were informed that their level of analgesia and respiratory rate would be continually assessed during the 24-h study period.

All patients were premedicated with midazolam (0.03 mg/kg) within 1 h before anesthetic induction and were hydrated with lactated Ringer's solution (12–15 mL/kg) before epidural catheter insertion at the L2–3 interspace. A T1–T4 sensory level to pinprick was achieved using 2% lidocaine with epinephrine (1:200,000). Small doses of midazolam (0.01–0.02 mg/kg intravenous) were used to provide intraoperative sedation. All medications, both intravenous and epidural, were withheld 30 min before the completion of surgery to ensure that patients were alert and had a regressing level of epidural blockade (T6–T8) on arrival in the Postanesthesia Care Unit (PACU). While in the PACU, patients were continuously monitored with electrocardiogram and pulse oximetry and followed up by one of the three nurse observers specifically assigned to the study.

At 10-min intervals, each patient was asked to indicate her level of pain intensity on a 10-cm visual analog scale (VAS) anchored with 0 representing "no pain" and 10 cm as "worst pain." When the patient first reported moderate postoperative discomfort (VAS $\geq$ 3 cm), a physician investigator slowly administered a single 10-mL epidural bolus of 30 μg sufentanil (Sufenta, Janssen Pharmaceutica, Piscataway, N.J.) (group A), 5 mg morphine sulfate (Duramorph, Elkins-Sinn, Inc., Cherry Hill, N.J.) (group B), or 30 μg sufentanil plus 3 mg morphine sulfate (group C) in a blinded fashion. Study solutions were prepared and delivered in unlabeled glass syringes by the Hospital Investigational Drug Service.

Patients remaining uncomfortable (VAS $\geq$ 3 cm) 20 min after receiving the epidural study narcotic were given a "rescue" bolus of fentanyl (50 μg) intravenously. Additional 50-μg boluses were administered every 15 min as required while the patient remained in the PACU. On transfer to the ward, patients were attached by an intravenous catheter to a PCA pump programmed to administer 1-mg doses of morphine with a 6-min lockout interval and a 4-h maximum dose of 30 mg. Patients were instructed to initiate PCA dosing when they experienced an unacceptable increase in the intensity of postoperative pain.

In addition to the pain intensity VAS, vital signs, level of sedation, the need for additional analgesic, and the incidence/severity of adverse effects were assessed at 5, 7, 10, 15, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, and 480 min after study drug administration and every 4 h thereafter. Visual analog scale pain scores were also measured immediately before initiation of PCA. Total PCA dose administered was recorded throughout the 24-h study period. When the nurse investigator was not at the bedside, the patient was continuously monitored via telemetry with a belt-impedance apnea monitor (Monotron, American Health Products Inc., Norwalk, Conn.).

Serial pain intensity VAS scores were used to determine the following: (a) *Onset* constituted the time until a reduction in pain intensity VAS of at least 1 cm occurred on two consecutive evaluations; (b) $T_{50\%}$ was the time until a pain intensity difference $\leq$50% of baseline VAS was reported; (c) T_{max} represented the time until the maximum pain intensity difference from baseline was achieved; and (d) *time to PCA (duration)* was the elapsed time between onset of epidural analgesia and patient initiation of PCA therapy.

The level of sedation was assessed using a ranked scale where 0 = alert; 1 = drowsy; 2 = very drowsy; 3 = very drowsy and disoriented; and 4 = stuporous. The percentage of patients with sedation scores $\geq$2 was tabulated. The percentages of patients with decreased respiratory rate (<10 beats/min), moderate to severe pruritus, or nausea and vomiting that required treatment with intravenous droperidol (0.625 mg) were also recorded.

Demographic variables and adverse effects within the three treatment groups were compared simultaneously via analysis of variance (continuous variables) or the χ^2 test (categorical variables). Baseline pain intensity was compared via one-way analysis of variance. For each computed parameter, the data were analyzed by analysis of covariance with subsequent pairwise comparisons of treatment groups analyzed with individual *t*-tests. Statistical tests with *P* values of 0.05 or less were considered to be statistically significant.

Results

All 45 patients enrolled in the study completed the entire protocol without significant complications. There were no significant differences among the three treatment groups with regard to patient demographics (Table 1). Likewise, there were no intergroup differences in time from completion of surgery to administration of study drug and in baseline pain intensity VAS score (*P* value not significant).

All treatment groups eventually achieved a very

Table 1. Summary of Demographic and Pretreatment Data

Parameter	Group A (sufentanil 30 μg)	Group B (morphine 5 mg)	Group C (combination)
No. patients entered	15	15	15
No. prematurely discontinued	0	0	0
ASA classification			
I	4 (26.7%)	3 (20.0%)	6 (40.0%)
II	11 (73.3%)	12 (80.0%)	9 (60.0%)
Age (yr)	43.4 ± 8.4	42.7 ± 6.8	42.8 ± 6.5
Weight (kg)	68.2 ± 14.0	67.5 ± 12.5	67.0 ± 13.9
Time to study drug administration (h)			
Mean ± SD	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.2
Median	0.5	0.6	0.6
Range	0.1–1.5	0.2–2.5	0.2–1.6
Baseline pain intensity (VAS cm)			
Mean ± SD	3.8 ± 1.6	3.5 ± 1.7	3.7 ± 1.5
Median	3.3	3.1	3.4
Range	2.9–7.6	2.7–7.6	2.9–7.9

For age and weight, values are expressed as mean ± SD.

Table 2. Summary of Effectiveness (time)

Parameter	Group A (sufentanil 30 μg)	Group B (morphine 5 mg)	Group C (combination)
Onset (h)			
Mean ± SD	0.1 ± 0.1	1.7 ± 1.4[a]	0.2 ± 0.3
Median	0.1	2.0	0.1
Range	0.1–0.6	1.0–4.0	0.1–1.0
$T_{50\%}$ (h)			
Mean ± SD	0.4 ± 0.8	2.1 ± 1.7[a]	0.6 ± 1.4
Median	0.1	2.0	0.1
Range	0.1–3.0	1.2–5.8	0.1–5.7
T_{max} (h)			
Mean ± SD	0.8 ± 0.7	5.9 ± 3.3[a]	0.8 ± 1.3
Median	0.6	4.0	0.5
Range	0.2–3.0	2.0–12.0	0.5–5.0
Time to PCA (duration) (h)			
Mean ± SD	3.4 ± 4.2	11.7 ± 8.9[a]	4.5 ± 5.3
Median	2.5	13.0	2.8
Range	1.0–17.6	2.0–23.3	0.9–18.9

[a] Significantly different compared with groups A and C ($P < 0.01$).

low level of pain intensity, albeit for varying periods of time. As noted in Table 2, both groups of patients who received sufentanil (A and C) had significantly faster onset ($P < 0.01$), $T_{50\%}$ ($P < 0.01$), and T_{max} ($P < 0.01$) than did the group that received morphine alone (group B). Figure 1 illustrates pain intensity VAS difference from baseline before initiation of PCA. Consistent with the faster onset of pain relief, a smaller proportion of patients in groups A and C required at least one rescue dose of fentanyl ($P < 0.01$) than that in group B ($P < 0.01$, Table 3).

Patients in groups A and C had a significantly shorter interval before initiating PCA (duration) than those in group B ($P < 0.01$). There was no significant difference in this interval between groups A and C (P value not significant, Table 2). Morphine requirements during the 3-h interval after initiation of PCA were significantly greater in group A than in either group C or group B ($P < 0.05$, Table 3). Group A also required significantly more PCA narcotic over the 24-h study period than groups B ($P < 0.01$) or C ($P < 0.05$).

Clinically significant respiratory depression was not observed. No patient experienced a decrease in oxygen saturation below 92% while monitored by pulse oximetry in the PACU. Continuous telemetric monitoring and nursing assessment of respiration did not detect a respiratory rate of 10 breaths/min or less

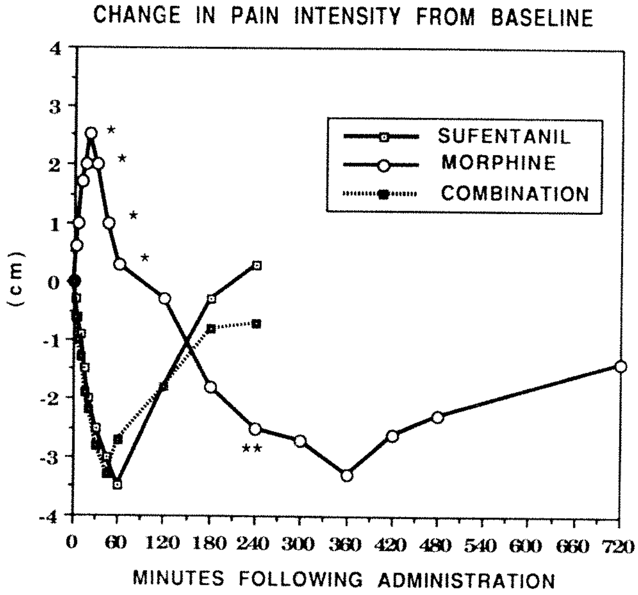


Figure 1. Change in mean pain intensity from baseline VAS scores during the first 12 h after epidural administration of study narcotic (values presented reflect scores before initiation of PCA). *Significant difference: group B (morphine) versus groups A and C (sufentanil, combination), $P < 0.05$. **Significant difference: group B (morphine) versus group A (sufentanil), $P < 0.05$.

in any patient during the 24-h study interval. There were no significant intergroup differences in the percentage of patients assigned sedation scores of 2 or greater (Table 4). Excessive sedation (i.e., score = 4) was not observed.

A large percentage of patients in each treatment group experienced either nausea/vomiting or pruritus during the study period (Table 4); however, significant intergroup differences in incidence were not observed.

Discussion

Patients who received single epidural bolus injections of sufentanil, morphine, or a combination of sufentanil plus morphine eventually achieved complete postoperative analgesia; however, significant intergroup differences were noted with regard to onset and duration of pain relief.

Sufentanil's ability to provide rapid and highly effective epidural analgesia was of particular benefit in the present study protocol where patients experienced the earliest aspects of postsurgical pain as their epidural anesthetic level regressed. In contrast, the delayed analgesic onset of epidurally administered morphine was associated with unacceptably high pain intensity scores that mandated intravenous administration of short-duration opioids. Such observations compare favorably with data previously reported by Van der Auwern and coworkers (16), who noted that the onset of postoperative analgesia with epidural sufentanil (50 μg) was four times as rapid but the duration only half as long as that provided by morphine (5 mg).

Consistent with previous investigations (9,10,16, 17), patients given sufentanil alone requested additional pain medication within 3–4 h after administration and required relatively large amounts of parenteral opioid during the remainder of the study period. In this regard, 24-h morphine PCA requirements were comparable to amounts self-administered by patients recovering from this form of surgery who had not received epidural analgesics (18).

The combination of lipophilic opioids and small amounts of morphine has been reported to provide highly effective epidural analgesia and either additive or supra-additive duration of activity. In two primary evaluations, Naulty and coworkers (11,14) found that epidural mixtures of either sufentanil or fentanyl plus morphine offered a more rapid onset and similar analgesic duration than larger doses of morphine in patients recovering from cesarean delivery. Likewise, Lema and Reiestad (13) reported that the combination of alfentanil and morphine (4 mg) provided a longer duration of postoperative pain relief and a lower incidence of side effects than 5 mg of morphine alone. In the present investigation, the combination of sufentanil and a 3-mg dose of morphine offered the benefits of a more rapid onset than morphine and lower 24-h parenteral narcotic requirement than a single dose of sufentanil; however, in contrast to the above studies, an additive duration of analgesia was not observed. This lack of potentiation is in agreement with the more recent findings of Cohen et al. (15) who reported shortened analgesic duration and an increased requirement for supplemental systemic opiates when patients given the combination of epidural morphine and fentanyl were compared with others treated with morphine alone.

The majority of patients in the combination group in the present study began self-administering PCA morphine during the analgesic trough between sufentanil's maximum reduction in pain intensity at 1 h and morphine's delayed maximal analgesic effect at 6 h. During this interval, patients needed to self-administer only minimal amounts of narcotic to reestablish effective pain relief as evidenced by their low 3-h PCA dose requirement. It is conceivable that a larger dose of sufentanil could have eliminated this "window" by extending the duration of epidural analgesia to a point that blended with the progressive increase in pain relief provided by morphine. In

Table 3. Narcotic Requirements

Parameter	Group A (sufentanil 30 μg)	Group B (morphine 5 mg)	Group C (combination)
% Requiring fentanyl "rescue"	0	73.3^a	13.3
Total PACU fentanyl (μg)	—	—	—
Mean ± SD	0	69.5^a	12.5
Median	0	50	0
Range	0	0–200	0–125
3-h PCA morphine (mg)			
Mean ± SD	16.8 ± 11.0^b	7.2 ± 6.1	7.5 ± 6.9
Median	15	6.5	7
Range	7.5–30.5	1–11	1–16.5
24-h PCA morphine (mg)			
Mean ± SD	45.5 ± 17.0^b	11.3 ± 13.8	25.5 ± 18.0
Median	39.3	7	20.5
Range	18–70	0–49	1–72.5

^{a}Significantly different compared with groups A and C ($P < 0.01$).
^{b}Significantly different compared with groups B and C ($P < 0.01$).
PACU, postanesthesia care unit; PCA, patient-controlled analgesia.

Table 4. Incidence of Adverse Events Before Initiation of Patient-Controlled Analgesia

	Group A (sufentanil 30 μg)		Group B (morphine 5 mg)		Group C (combination)		
Parameter	*n*	%	*n*	%	*n*	%	*P* value
Sedation score ≥2	2	13.4	3	20.0	2	13.4	NS
Respiratory depression	0	—	0	—	0	—	NS
Nausea and vomiting	8	53.3	5	33.3	9	60.0	NS
Pruritus	3	20.0	5	33.3	7	46.7	NS

NS, not significant.

patients recovering from cesarean delivery (9) or general surgery (10,17), increasing the sufentanil dose from 25 to 70 μg resulted in a respective increase in analgesic duration from 3 to 5 h. Nevertheless, a high degree of caution must be exercised when employing larger doses of sufentanil because a number of "immediate-onset" respiratory arrests have been reported with epidural boluses greater than 50 μg (17,19).

The incidence and severity of troublesome side effects associated with epidural morphine appear to be related to increases in dose (1,5). Previous combination studies (11,13) employing lower doses of morphine (under 5 mg) have reported a reduced occurrence of nausea and pruritus. However, despite a 40% reduction in dose, patients in group C receiving sufentanil plus morphine had an incidence of adverse events similar to those receiving morphine alone.

In conclusion, the epidural administration of a combination of sufentanil and morphine offered the advantages of either more rapid onset or reduced requirement for self-administered narcotic than respective doses of morphine or sufentanil alone in patients recovering from intraabdominal gynecologic surgery. Although not providing an additive duration of analgesia, the mixture appears to be useful in settings where an established pain stimulus must be rapidly attenuated. Methods of further extending duration of pain relief, including the use of larger doses of morphine or sufentanil, should be evaluated.

The authors thank Linda Preble, RN, MPS, Cathy Curran, RN, and Gina Revezi, RN, for their help with data collection.

References

1. Rawal N, Sjöstrand VH, Dahlström B, Nydahl Per A, Östelius J. Epidural morphine for postoperative pain relief: a comparative study with intramuscular narcotic and intercostal block. Anesth Analg 1982;61:93–8.
2. Rosen MA, Hughes SC, Shnider SM, Abboud TK. Epidural morphine for the relief of postoperative pain after cesarean delivery. Anesth Analg 1983;62:666–72.

3. Loper KA, Ready LB. Epidural morphine after anterior cruciate ligament repair: a comparison with PCA morphine. Anesth Analg 1989;68:350–2.
4. Nordberg G, Hedner T, Mellstrand T. Pharmacokinetics of epidural morphine in man. Eur J Clin Pharmacol 1984;26: 233–7.
5. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
6. Kafer ER, Brown JT, Scott DD. Biphasic depression of ventilatory responses to CO_2 following epidural morphine. Anesthesiology 1983;58:418–27.
7. Etches RC, Sandler A, Daley MD. Respiratory depression and spinal opioids. Can J Anaesth 1989;36:165–85.
8. Naulty JS, Datta S, Ostheimer GW, Johnson M. Epidural fentanyl for postcesarean delivery pain management. Anesthesiology 1985;63:694–8.
9. Rosen MA, Dailey PA, Hughes SC, Shnider SM, Abboud TK. Epidural sufentanil for postoperative analgesia after cesarean section. Anesthesiology 1985;68:448–54.
10. Donadoni R, Rolly G, Noordvin H. Epidural sufentanil for postoperative pain relief. Anaesthesia 1985;40:634–8.
11. Naulty JS, Parmet J, Pate A, Becker R, Loeffler C, Barnes D. Epidural sufentanil and morphine for post-cesarean delivery analgesia. Anesthesiology 1990;73:A965.
12. Boersma FP, Noonduin H, Pieters W, Woestenborgs R, Heykarts J. Sufentanil concentrations in the spinal cord after long-term epidural infusion. Anesthesiology 1989;71:A706.
13. Lema MJ, Reiestad F. A comparison of epidural alfentanil, morphine and alfentanil morphine combination for postoperative analgesia at total hip replacement. Anesthesiology 1989; 71:A702.
14. Naulty JS, Ross R. Epidural fentanyl and morphine for post-cesarean delivery analgesia. Proc Soc Obstet Anesth Perinatol 1988;20:178.
15. Cohen SE, Subak LL, Brose WG, Halpern J. Analgesia following cesarean section: comparison of five opioid techniques. Anesthesiology 1989;71:A832.
16. Van der Auwern A, Venborgh C, Camu F. Analgesic and cardiorespiratory effects of epidural sufentanil and morphine. Anesth Analg 1987;66:999–1003.
17. Graf G, Frasca A, Sinatra R, Silverman DG. Optimizing postoperative analgesia with a rapidly acting epidural narcotic: results of a prospective randomized double blinded study. Anesthesiology 1988;69:A338.
18. White PF. Use of patient controlled analgesia for management of acute pain. JAMA 1988;259:243–7.
19. Blackburn C. Respiratory arrest after epidural sufentanil. Anaesthesia 1987;42:665–6.

Effects of Clear Liquids on Gastric Volume and pH in Healthy Volunteers

Ketan Shevde, MD, and Narendra Trivedi, MD

SHEVDE K, TRIVEDI N. Effects of clear liquids on gastric volume and pH in healthy volunteers. Anesth Analg 1991; 72:528–31.

The effects of clear liquids on gastric volume and pH were examined in 30 healthy ASA physical status I volunteers. After overnight fasting, a Salem-sump nasogastric tube was inserted and gastric contents were removed for measurement of volume and pH. Gastric contents were then reinserted through the nasogastric tube into the stomach. The volunteers were randomly divided into three groups: group 1 (n = 10) received 240 mL water, group 2 (n = 10) received 240 mL coffee, and group 3 (n = 10) received 240 mL pulp-free orange juice. All liquids were administered orally. Gastric contents were then again aspirated, measured for volume and pH, and reinserted through the nasogastric tube every half hour until gastric volume was <25 mL. All volunteers had gastric volumes <25 mL with a slight decrease in pH within 2 h of orally taking one of the three 240-mL liquids. These data suggest that if patients have ingested a moderate amount of clear liquids it is safe to conduct general anesthesia after a 2-h fast in healthy surgical patients.

Key Words: GASTROINTESTINAL TRACT, STOMACH—pH and volume with fasting.

Outpatient anesthesia is becoming increasingly important in clinical practice in response to recent cost-containment pressures. At times, patients scheduled for outpatient surgery do not comply with instructions regarding fasting and ingest liquids preoperatively. In such cases, the anesthesiologist is in a dilemma as to a safe time for induction of anesthesia without undue risk of vomiting with aspiration of stomach contents.

The current recommendations for fasting before elective surgery are based on a gastric emptying time for solids that is generally considered to be 8 h (1). It is well known that water either passes through the stomach or is absorbed very rapidly. A recent study showed that half of 750 mL of water ingested disappears from the stomach in 20 min (2). Thus, it may not be necessary to wait 8 h before induction of anesthesia after ingestion of clear liquids. We therefore conducted a prospective randomized study in healthy volunteers to assess gastric emptying time, changes in gastric volume, and pH after ingestion of water, black coffee, and pulp-free orange juice.

Methods

The study was approved by the hospital's human research committee, and informed written consent was obtained from 30 healthy volunteers, ASA physical status I. Volunteers with a history of gastrointestinal problems, pregnancy, gastric surgery, smoking, or alcoholism, and those taking medications were not included in the study because we intended the study to address the issue as regards relatively healthy patients. During the study period, the volunteers were allowed to move about freely, watch television, listen to music, or lie down and relax in an easy chair, so that they felt comfortable. We do not routinely premedicate ambulatory surgical patients; therefore, our volunteers were not premedicated.

After an overnight fast, an 18F Argyle Salem Sump nasogastric tube was gently inserted through the nose into the stomach after local application of lidocaine viscous jelly. The position of the nasogastric tube was confirmed by auscultation over the stomach while air was inserted through the tube with a syringe. Air was then allowed to escape through the open nasogastric tube, and the tube was taped to the side of the nose. Using a 60-mL Toomey syringe, gastric contents were then aspirated through the nasogastric tube with volunteers in the supine, sitting, and both lateral and head-down positions to

---

Received from the Department of Anesthesiology, Maimonides Medical Center, Brooklyn, New York. Accepted for publication November 26, 1990.

Address correspondence to Dr. Shevde, Department of Anesthesiology, Maimonides Medical Center, 4802 Tenth Avenue, Brooklyn, NY 11219.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Demographic Data

	Group 1 (water)	Group 2 (coffee)	Group 3 (orange juice)	Statistical significance
Age (yr)	30.7 ± 5.9	30.4 ± 9.9	30.3 ± 6.4	NS
Height (cm)	172.2 ± 10.9	169.4 ± 5.6	171.2 ± 6.1	NS
Weight (kg)	73.5 ± 16.5	68.6 ± 13.7	72.9 ± 11.3	NS
Sex (M/F)	7/3	6/4	6/4	
Fasting time (h)	11.7 ± 1.1	12.3 ± 1.8	11.7 ± 1.6	NS

NS, no statistically significant differences.
Except for sex, values are expressed as mean ± SD.

Table 2. Gastric Volume

	Group 1 (water)		Group 2 (coffee)		Group 3 (orange juice)		
Time	Vol	*n*	Vol	*n*	Vol	*n*	Statistical significance
Baseline value	33.3 ± 26.3	10	26.5 ± 17.7	10	23.0 ± 11.6	10	NS
30 min	45.5 ± 44.9	10	48.8 ± 39.4	10	93.5 ± 53.5	10	NS
60 min	31.6 ± 15.2	8	34.9 ± 24.1	9	46.5 ± 31.0	10	NS
90 min	25.0 ± 7.1	2	27.3 ± 24.5	6	27.4 ± 27.1	8	NS
120 min	17.5 ± 3.5	2	19.0 ± 5.7	2	20.0 ± 1.1	2	NS

Vol, volume; *n*, number of volunteers; NS, not statistically significant.
Values for volumes are expressed as mean ± SD.

maximize stomach emptying. The volume of gastric contents and pH were measured. These values were considered to be baseline values.

After aspiration of the gastric contents and measurement of volume and pH, the gastric contents were then reinserted into the stomach through the nasogastric tube while volunteers were asked to keep their eyes closed to avoid possible unpleasant psychological effects of reinsertion.

Volunteers were then randomly divided into three groups. Group 1 ($n = 10$) received 240 mL water (pH 6.0–6.20), group 2 ($n = 10$) received 240 mL black coffee (pH 4.80–5.00), and group 3 ($n = 10$) received 240 mL pulp-free orange juice (pH 3.30–3.50). All three liquids were given orally over 5 min. After this, gastric contents were aspirated in a similar fashion as described, analyzed for volume and pH, and reinserted through the nasogastric tube at 30-min intervals until the gastric volume was less than 25 mL.

The pH of the gastric contents was measured by an Ohio PHH-44 pH meter that has an accuracy of within 0.01 (with temperature correction) and that was calibrated against known solutions of pH 4 and 7 at the beginning of each study. Statistical analysis was performed with an analysis of variance test, and P values <0.05 were considered to be statistically significant. The data are presented as mean ± SD.

Results

There were no significant differences between the groups with respect to age, sex, weight, height, and fasting times (Table 1). We were able to obtain gastric fluid from all of the volunteers after overnight fasting. The baseline gastric volumes—33.3 ± 26.3 mL in group 1 (water), 26.5 ± 17.7 mL in group 2 (coffee), and 23.0 ± 11.6 mL in group 3 (orange juice)—were not significantly different (Table 2). The baseline pH was 2.45 ± 1.7 in group 1, 2.07 ± 1.0 in group 2, and 2.13 ± 1.2 in group 3 (Table 3), also not statistically significantly different. Twenty-three of 30 (77%) volunteers had baseline gastric pH levels <2.5; 13 (43%) of the volunteers had baseline gastric volume >25 mL. Nine (30%) of the volunteers had both gastric volumes >25 mL and pH levels <2.5. After oral fluid intake, gastric volume increased in all three groups with a slight decrease in pH (Tables 2 and 3), but all volunteers had gastric volume <25 mL within 2 h (Figure 1).

Discussion

One of the most significant complications associated with the induction of anesthesia is pulmonary aspiration of vomited or regurgitated stomach contents. The risk of aspiration and the severity of lung damage

Table 3. Gastric pH

Time	Group 1 (water) pH	n	Group 2 (coffee) pH	n	Group 3 (orange juice) pH	n	Statistical significance
Baseline value	2.45 ± 1.7	10	2.07 ± 1.0	10	2.13 ± 1.2	10	NS
30 min	2.05 ± 1.5	10	1.87 ± 0.9	10	2.49 ± 0.8	10	NS
60 min	1.58 ± 0.2	8	2.03 ± 1.7	9	1.69 ± 0.6	10	NS
90 min	1.45 ± 0.2	2	1.34 ± 0.1	6	1.51 ± 0.4	8	NS
120 min	1.31 ± 0.2	2	1.25 ± 0.2	2	1.54 ± 0.5	2	NS

n, number of volunteers; NS, not significant.
Values for pH are expressed as mean ± SD.

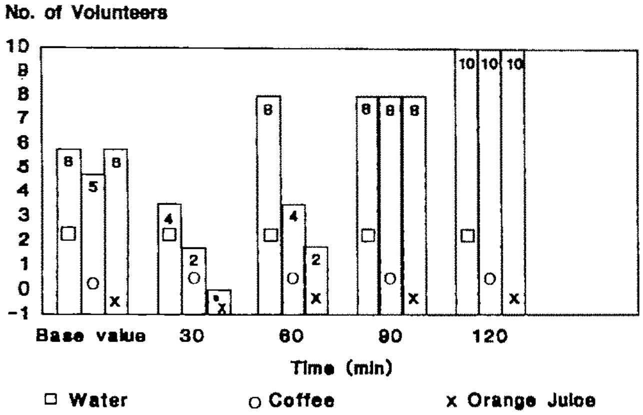


Figure 1. Number of volunteers with gastric volume <25 mL.

are considered to be enhanced when the pH of the aspirate is <2.5 and the volume is >25 mL (3,4). Anesthesiologists usually advise patients to refrain from oral intake for at least 8 h before induction of anesthesia to prevent this complication. With the recent increase in day surgery and same-day admissions for nonambulatory procedures, a large number of patients come to the hospital without having seen an anesthesiologist, and some of them have not complied with the 8-h fasting order. This presents the anesthesiologist with a dilemma as to whether to postpone the case to another day, thus causing inconvenience to the patient, surgeon, and the operating room staff, or to proceed with surgery with the possibility of aspiration.

Our study was designed to determine the fasting time necessary for safe induction of anesthesia in patients who may not have complied with fasting instructions and consumed water, coffee, or orange juice shortly before surgery. We used an 18F Salem Sump nasogastric tube for aspiration of gastric contents. This is a valid and well-accepted method for assessment of gastric volumes (5). By reinserting the gastric contents into the stomach, we were able to estimate accurately the volume at subsequent 30-min intervals. To avoid possible psychological effects, we asked the volunteers to keep their eyes closed during reinsertion of gastric fluid. Also, we allowed volunteers to move about freely, watch television, listen to music, or lie down and relax in an easy chair to make them feel comfortable and to mimic preoperative ambulatory surgical conditions.

Our study confirmed the results of previous studies (6–8) that even after 11–13 h of fasting, a large number of patients had gastric pH <2.5 and gastric volume >25 mL. Recent studies in children have shown that preoperative oral liquid intake reduces morbidity significantly without significant changes in gastric volume and pH (9,10), and in adults a breakfast of tea and toast 2–3 h before surgery has been shown to be associated with gastric volumes and pH levels similar to those observed in patients that fasted for 13 h (11).

In all 30 of our volunteers, we found that a 2-h period was all that was necessary for the volume of stomach content to return to <25 mL after ingestion of moderate amounts of clear liquids. The study was not designed to include coffee with milk because milk curdles in the stomach and may act in a manner similar to that of solids.

On the basis of the present data it would seem appropriate that in cases in which patients have ingested moderate amounts of clear fluids, it is safe to conduct general anesthesia after 2 h in otherwise healthy surgical patients. This will allow greater flexibility in the management of ambulatory patients. We caution that patients who are at higher risk for aspiration such as diabetics, pregnant women, and obese patients should wait the customary 8 h before induction of anesthesia as commonly recommended.

In making the above recommendations, the authors recognize that the present study has certain limitations. Further studies will be necessary, for example, to determine whether coffee with milk or water and oral medications will be as safe. We have used the word "clear" to exclude liquids with suspensions (such as juice with pulp) or those that may form solids in the stomach such as milk. This was done mainly because fasting guidelines are available for solids but not for clear liquids. In our study we also assumed that solid particles may have interfered with our ability to empty the stomach completely. We appreciate that volunteers do not mimic the patient population precisely, but we believe that they are similar to a large proportion of ambulatory patients. The study specifically called for aspiration of stomach contents at half-hour intervals because the question we wanted to answer was not *if* it is safe to anesthetize patients after a given time, but rather *when* is it safe to anesthetize patients after they have ingested a moderate amount of clear liquids. Because there was a substantial decrease in the gastric volume after the first aspirate at 30 min, we do not believe that aspiration and reinsertion of gastric contents by themselves stimulated gastric emptying. We believe that the specific question "When is it safe?" could only be answered with the method used. With this study we feel comfortable that this question has been satisfactorily answered and that waiting beyond 2 h after ingestion of moderate amounts of clear liquids is not necessary for safe anesthetic induction.

References

1. Barash P, Cullen B, Stoelting R. Clinical anesthesia. 1st ed. Philadelphia: JB Lippincott, 1989:1123.
2. Moore JG, Christian PE, Coleman RE. Gastric emptying of varying meal weight and composition in man: evaluation by dual liquid and solid phase method. Dig Dis Sci 1981;26:16–22.
3. Teabeaut JR II. Aspiration of gastric contents: an experimental study. Am J Pathol 1952:28:51–63.
4. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1946: 52:191–205.
5. Hardy J, Plourde G, Lebrun M, et al. Determining gastric contents during general anaesthesia: evaluation of two methods. Can Anaesth Soc J 1987;34:474–7.
6. Coombs DW, Hooper D, Colton J. Acid aspiration prophylaxis by use of pre-operative oral administration of cimetidine. Anesthesiology 1979;51:352–6.
7. Kirkegaard P, Sorensen O, Kirkegaard P. Cimetidine in the prevention of acid aspiration during anaesthesia. Acta Anaesthiol Scand 1980;24:58–60.
8. Hester JB, Heath ML. Pulmonary acid aspiration syndrome: should prophylaxis be routine? Br J Anaesth 1977;49:595–9.
9. Splinter WM, Stewart JA, Muir JG. Large volumes of apple juice pre-operatively do not affect gastric pH and volume in children. Can J Anaesth 1990;37:36–9.
10. Schreiner MS, Triebwasser A, Keon T. Ingestion of liquids compared with pre-operative fasting in pediatric outpatients. Anesthesiology 1990;72:593–7.
11. Miller M, Wishart HY, Nimmo WS. Gastric content at induction of anaesthesia: is a 4 hour fast necessary? Br J Anaesth 1983;55:1185–8.

Effects of H_2-Receptor Blockers on Response of Cerebral Blood Flow to Normocapnic Hypoxia

G. Audibert, MD, C. Saunier, MD, D. Hartemann, PhD, O. Bigard, MD, and J. P. Haberer, MD

AUDIBERT G, SAUNIER C, HARTEMANN D, BIGARD O, HABERER JP. Effects of H_2-receptor blockers on response of cerebral blood flow to normocapnic hypoxia. Anesth Analg 1991;72:532–7.

Cimetidine blunts the increase in cerebral blood flow (CBF) normally observed during hypoxia. It is important, therefore, to know whether other H_2-blockers also affect the cerebral circulation adaptation to hypoxia. Cerebral blood flow was measured in 24 awake dogs after an intravenous injection of either saline (control) or one of three H_2-blockers: 1 mg/kg ranitidine, 0.4 mg/kg famotidine, or 1 mg/kg roxatidine. These doses are equipotent blockers of H_2-gastric receptors. Each dog was studied during normoxia and after 2 and 4 h of normocapnic hypoxia (F_{IO_2}, 0.10; F_{ICO_2}, 0.035). During each set of experimental conditions, a bolus of either saline or one of the anti-H_2 drugs was administered, and, 15 min later, radiolabeled microspheres (ruthenium 103, scandium 46, and cerium 141) were injected into the left atrium for measurement of regional CBF. After death by an overdose of thiopental, each dog's brain was excised and fixed in 10% formaldehyde; it was then weighed and dissected by region, with the radioactivity measured in each region using a gamma counter. During hypoxia, Pa_{O_2} ranged from 45 to 50 mm Hg, and pH, Pa_{CO_2}, and hematocrit were within the normal limits. In the control group CBF increased 34% above normoxic baseline levels after 2 h and 31% after 4 h of hypoxia. Ranitidine (1 mg/kg) did not prevent the increase in CBF during hypoxia, but famotidine and roxatidine prevented it. When the dose of ranitidine was doubled (2 mg/kg), it too abolished the increase of CBF induced by hypoxia. In conclusion, H_2-receptor blockers could interfere with the adaptation of CBF during hypoxia.

Key Words: BRAIN, BLOOD FLOW—H_2-receptor blockers. HISTAMINE, H_2-RECEPTOR BLOCKERS—ranitidine, famotidine, roxatidine.

H_2-blockers are frequently used in gastroenterology, intensive care, and anesthesiology. In anesthesiology, they are used to limit the deleterious effect of gastric content aspiration. Their use for this purpose means that their pharmacologic effects would be present should the patient become hypoxic. The distribution of peripheral blood flow is significantly altered by hypoxia. For instance, cerebral blood flow (CBF) increases when the partial pressure of oxygen in arterial blood decreases below 60 mm Hg (1) as a compensatory mechanism to maintain oxygenation of the brain. Alteration of activity of type 2 histamine receptors (H_2) in the brain may affect CBF responses to hypoxia. For example, H_2-receptors on blood vessels have been identified in the brains of animals (2), and mastocytes containing histamine exist in the vicinity of the cerebral vessels (3). In addition, pharmacologically active doses of histamine increase CBF by acting on H_2-receptors (4). Moreover, a recent work in vitro demonstrates the attenuation by cimetidine of the relaxation induced by histamine of cerebral artery strips partially contracted with prostaglandin $F_{2\alpha}$ (5).

In a previous study, Clozel et al. showed that cimetidine almost completely inhibits the increase in CBF associated with hypoxia in the awake dog (6). The aim of the present work was to examine, using the same model as that used by Clozel et al., the effect on the CBF response to hypoxia of three other H_2-inhibitors administered in therapeutic doses: namely, ranitidine, famotidine, and roxatidine.

Methods

Twenty-four beagle dogs weighing 13.5 ± 0.6 kg (mean ± SEM) were divided into four groups of six dogs each: control dogs, and those given ranitidine,

---

Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1989.

Received from INSERM U14, Vandoeuvre-les-Nancy, France; and the Département d'Anesthésiologie, Université de Nancy, Nancy, France. Accepted for publication November 23, 1990.

Address correspondence to Dr. Saunier, INSERM U14, Plateau de Brabois, C.O. No. 10,54500, Vandoeuvre-les-Nancy, France.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

famotidine, or roxatidine. Fifteen days before each experiment, the dogs were anesthetized with intravenous thiopental (25 mg/kg) and curarized with vecuronium (0.1 mg/kg) for insertion of polyvinyl catheters, one in the external jugular vein for injection of the drugs to be tested, one in the abdominal aorta via the femoral artery attached to a syringe for reference flow and arterial blood sampling, and one in the left atrium after thoracotomy in the fifth left intercostal space. Temporary thoracic drainage was carried out immediately after the intervention and left in place for 12 h. The loose ends of the three catheters were tunneled under the skin and brought out behind the nape of the neck where the catheters were protected by a dressing and a collar. Local and general antibiotics were then given for several days. The experiments were performed according to standards for laboratory animal care.

On the day of the experiment, when rectal temperatures were about 38°C, the dogs were studied while awake and breathing spontaneously. The first series of measurements were performed during normoxia (atmospheric air). The drug to be tested was randomly injected into the jugular vein, i.e., either 1 mg/kg ranitidine, 0.4 mg/kg famotidine, or 1 mg/kg roxatidine; these doses are equipotent in their effects on the H_2-gastric receptors (7–9). After these experiments, a double dose (2 mg/kg) of ranitidine was used in three additional animals with the same protocol. The control dogs received saline (1 mL IV). Aortic pressure was measured with an external transducer placed at the level of the animal's heart, recorded, and averaged (Gould). Blood samples were taken from the arterial catheter to measure pH, Pao_2, $Paco_2$ (Radiometer, ABL 30), hemoglobin concentration, and oxygen saturation (Sao_2) (Radiometer OSM2). Fifteen minutes after the injection of one randomized drug, microspheres were injected for the measurement of CBF (see below). The volume of blood taken for measurement was replaced by saline (10).

The dog was then placed in a 45-m^3 room containing a gas mixture of 10% oxygen, 3.5% CO_2, and 86.5% nitrogen. The addition of 3.5% CO_2 prevented the development of hypocapnia associated with hyperventilation, which otherwise would decrease CBF. Room temperature was maintained at 21°C and humidity at 50% by air-conditioning. The second and third series of measurements were performed after 2 and 4 h of normocapnic hypoxia.

Radiolabeled Microspheres Technique

This technique used microspheres of styrene divinyl copolymer, 15 μm in diameter (New England Nuclear), labeled by the radionuclides cerium 141, ruthenium 103, and scandium 46 (11). Before each injection, after mechanical agitation (Vortex), the microspheres were separated by sonication (Bransonic 32) for 30 min. Finally, a further mechanical agitation (Vortex) was carried out immediately before injection of 1 mL homogeneous suspension in 10% dextran and 0.01% Tween 80 into the left atrial catheter (1–2 million microspheres). To assure complete injection of the microspheres, the syringe and the catheter were flushed with 10 mL saline. The order of the injection of isotopes was randomly chosen before each experiment. A reference blood sample was taken from the aorta at a constant flow of 4.4 mL/min over 2 min, before, during, and after the injection of microspheres.

At the end of the experiment, the animal was killed with a lethal dose of thiopental. The brain was immediately removed and fixed in 10% formaldehyde solution. After 2 days, it was dissected according to a rigorous scheme allowing 38 samples to be obtained. These were counted in a gamma counter (Packard Autogamma 800 C) with three windows adjusted for the characteristic energy peaks of the three isotopes. The arterial reference samples were similarly counted. The counts per minute recorded with each window were corrected for overlap with the other two isotopes by a computer program. The absolute regional blood flows were expressed per 100 g of tissue. The cerebral oxygen supply was computed as the product of the arterial O_2 content per milliliter and the total CBF. The arterial O_2 content (Cao_2: mL O_2/mL blood) was computed according to the following formula: $[Hb]\ g \cdot mL^{-1} \times 1.37 \times Sao_2\%$. The results were expressed as mean value ± standard error of the mean (SEM). The changes from normoxia to hypoxia were expressed as the average value of the percent variation of each variable.

The statistical analysis used two-factor two-tailed variance analysis. The differences were tested by using Student's *t*-test. Differences were considered as statistically significant when the *P* value was <0.05.

Results

At each time period, $Paco_2$ and pH values did not differ significantly between experimental groups (Table 1). During hypoxia, $Paco_2$ was comparable to its value during normoxia (29–34 mm Hg) despite hyperventilation, owing to the inhaled CO_2. Hypoxia was moderate (Pao_2 about 50 mm Hg), with decreases in arterial saturation and Cao_2 of about 20% in all four groups.

Table 1. Arterial Blood Gas Tensions and Acid-Base Values

	Air	Hypoxia 2 h	Hypoxia 4 h
pH			
Control	7.430 ± 0.007	7.406 ± 0.008	7.403 ± 0.008
Ranitidine[a]	7.382 ± 0.010	7.350 ± 0.006	7.348 ± 0.007
Famotidine[b]	7.412 ± 0.010	7.420 ± 0.006	7.417 ± 0.006
Roxatidine[c]	7.434 ± 0.009	7.439 ± 0.007	7.440 ± 0.008
$Paco_2$ (mm Hg)			
Control	30.9 ± 1.2	32.5 ± 0.9	32.4 ± 1.0
Ranitidine	30.6 ± 0.5	34.5 ± 1.0	34.5 ± 1.2
Famotidine	29.7 ± 1.6	29.6 ± 1.0	29.6 ± 0.8
Roxatidine	35.9 ± 0.7	33.8 ± 0.5	33.2 ± 0.5
Pao_2 (mm Hg)			
Control	82.0 ± 5.2	44.6 ± 1.6	44.9 ± 1.6
Ranitidine	81.6 ± 2.5	50.0 ± 2.0	49.6 ± 1.2
Famotidine	86.1 ± 1.2	46.9 ± 0.7	45.0 ± 1.0
Roxatidine	87.6 ± 1.5	47.3 ± 0.4	48.7 ± 0.2
Sao_2 (%)			
Control	95.0 ± 0.8	76.4 ± 0.9	75.7 ± 1.3
Ranitidine	94.8 ± 0.7	76.0 ± 2.2	74.7 ± 1.8
Famotidine	96.1 ± 0.4	80.3 ± 0.5	77.5 ± 0.9
Roxatidine	95.8 ± 0.8	79.9 ± 1.1	80.2 ± 0.7
Cao_2 (mL/100 mL)			
Control	15.7 ± 1.0	12.9 ± 1.1	12.6 ± 1.1
Ranitidine	15.6 ± 1.5	13.3 ± 1.1	12.8 ± 1.0
Famotidine	17.2 ± 0.9	14.4 ± 0.9	13.8 ± 0.9
Roxatidine	18.7 ± 1.2	16.0 ± 0.9	15.9 ± 1.0

Values are expressed as mean ± SEM; $n = 6$.
The values of Pao_2, Sao_2, and Cao_2 differed statistically ($P < 0.001$) during hypoxia from the values in air.
[a] Dose of ranitidine was 1 mg/kg.
[b] Dose of famotidine was 0.4 mg/kg.
[c] Dose of roxatidine was 1 mg/kg.

Table 2. Hemodynamic Data

	Air	Hypoxia 2 h	Hypoxia 4 h
Heart rate (beats/min)			
Control	116 ± 6	122 ± 7	128 ± 9
Ranitidine	110 ± 8	115 ± 10	114 ± 11
Famotidine	103 ± 6	119 ± 7[a]	115 ± 8
Roxatidine	111 ± 5	130 ± 12	123 ± 12
MAP (mm Hg)			
Control	124 ± 3	135 ± 4[a]	138 ± 4[a]
Ranitidine	118 ± 7	131 ± 7[b]	128 ± 9[a]
Famotidine	117 ± 6	123 ± 4[c]	125 ± 3[c]
Roxatidine	120 ± 2	132 ± 2[b]	128 ± 3[a,c]

MAP, mean arterial pressure.
All values are expressed as mean ± SEM; $n = 6$.
All doses as in Table 1.
[a] $P < 0.05$ versus values for air in the same group.
[b] $P < 0.01$ versus values for air in the same group.
[c] $P < 0.05$ versus control values during the same period.

The hemodynamic variables are shown in Table 2. Heart rate was relatively stable in all groups except the famotidine group. In the control, ranitidine, and roxatidine groups, hypoxia was accompanied by a slight increase in mean arterial pressure.

The results of CBF measurements are given as absolute values in Table 3 and as percent of control air values in Figure 1. In the control group, hypoxia was associated with 34% and 31% increases in CBF after the second and fourth hours of hypoxia (Figure 1). The increase in CBF was observed in all regions of the brain, varying from 26% to 69% of the value during normoxia. The maximum increase in CBF was observed in the brainstem (medulla oblongata, pons, and cerebral peduncles) and the hypothalamus: in these four areas, the increase in CBF varied from 37% to 69% at the second hour and 48% to 68% at the fourth hour. In contrast, the cortical regions showed a smaller range of changes in blood flow, 26%–36%. These changes in CBF allowed the oxygen supply to the brain to remain constant: the decrease in Cao_2 was compensated for by the increase in blood flow (Figure 1).

Famotidine blocked the adaptation of the cerebral circulation to hypoxia. This blockade occurred in all areas of the brain; the partial preservation of CBF in the brainstem (+15% after 2 h and +19% after 4 h) was not statistically significant. The result of these changes was a 17% decrease in oxygen transport during both periods of hypoxia, significantly less

Table 3. Regional Cerebral Blood Flows (mL·min^{-1}·100 g^{-1}) During Air Breathing and During 2 and 4 h Hypoxia Alone (Control) and With Ranitidine, Famotidine, or Roxatidine

	Air	Hypoxia 2 h	Hypoxia 4 h
Medulla oblongata			
Control	53 ± 5	70 ± 5	78 ± 6
Ranitidine	49 ± 4	70 ± 7	66 ± 7
Famotidine	61 ± 7	63 ± 10	69 ± 7
Roxatidine	66 ± 5	69 ± 6	73 ± 5
Pons			
Control	60 ± 6	84 ± 4	91 ± 9
Ranitidine	50 ± 3	71 ± 6	67 ± 6
Famotidine	66 ± 7	69 ± 10	75 ± 7
Roxatidine	68 ± 6	73 ± 5	76 ± 2
Cerebral peduncles			
Control	93 ± 1	130 ± 6	140 ± 14
Ranitidine	90 ± 9	131 ± 14	121 ± 13
Famotidine	102 ± 12	113 ± 21	120 ± 16
Roxatidine	95 ± 7	98 ± 8	97 ± 5
Frontal and olfactory lobes			
Control	100 ± 9	135 ± 9	126 ± 12
Ranitidine	84 ± 9	115 ± 12	104 ± 8
Famotidine	101 ± 9	101 ± 16	102 ± 10
Roxatidine	105 ± 6	103 ± 6	79 ± 5
Temporal lobe			
Control	85 ± 8	106 ± 8	106 ± 9
Ranitidine	76 ± 6	105 ± 10	93 ± 6
Famotidine	94 ± 10	90 ± 10	94 ± 10
Roxatidine	86 ± 6	87 ± 5	79 ± 5
Corpus callosum			
Control	40 ± 2	54 ± 5	54 ± 3
Ranitidine	45 ± 4	64 ± 5	54 ± 3
Famotidine	56 ± 3	58 ± 5	58 ± 5
Roxatidine	58 ± 3	53 ± 5	55 ± 4
Hippocampus			
Control	75 ± 6	103 ± 4	101 ± 10
Ranitidine	62 ± 6	86 ± 9	78 ± 6
Famotidine	81 ± 5	81 ± 9	81 ± 5
Roxatidine	85 ± 5	83 ± 5	79 ± 5
Hypothalamus			
Control	78 ± 18	113 ± 9	119 ± 19
Ranitidine	81 ± 8	119 ± 9	107 ± 12
Famotidine	92 ± 11	86 ± 12	94 ± 8
Roxatidine	103 ± 10	106 ± 9	112 ± 10
Thalamus			
Control	123 ± 13	160 ± 10	166 ± 10
Ranitidine	87 ± 9	124 ± 17	113 ± 10
Famotidine	108 ± 10	113 ± 19	113 ± 17
Roxatidine	111 ± 6	110 ± 5	109 ± 10
Parietal lobe			
Control	102 ± 16	123 ± 6	128 ± 12
Ranitidine	102 ± 5	136 ± 10	125 ± 8
Famotidine	124 ± 10	121 ± 14	120 ± 7
Roxatidine	113 ± 6	111 ± 7	103 ± 5
Occipital lobe			
Control	108 ± 13	138 ± 15	137 ± 16
Ranitidine	108 ± 9	155 ± 13	132 ± 9
Famotidine	120 ± 12	127 ± 18	125 ± 9
Roxatidine	119 ± 7	113 ± 9	103 ± 8
Cerebellum			
Control	77 ± 8	101 ± 9	105 ± 10
Ranitidine	87 ± 8	104 ± 13	110 ± 11
Famotidine	107 ± 1	104 ± 11	108 ± 9
Roxatidine	99 ± 6	105 ± 8	106 ± 7
Total brain			
Control	89 ± 9	115 ± 8	115 ± 8
Ranitidine	83 ± 6	115 ± 10	103 ± 7
Famotidine	100 ± 8	99 ± 13	100 ± 7
Roxatidine	98 ± 4	98 ± 5	92 ± 5

Values are expressed as mean ± SEM; $n = 6$. Doses as in Table 1.

In control and ranitidine groups, all values during hypoxia differed statistically ($P < 0.05$ or less) from the values in air. The differences were not significant in famotidine and roxatidine groups.

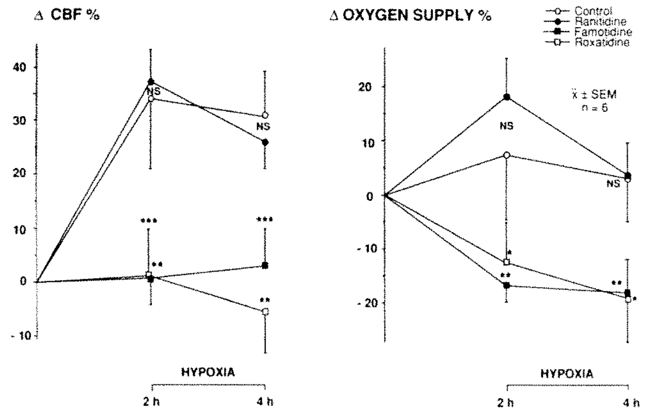


Figure 1. Changes in total cerebral blood flow (ΔCBF %) after 2 and 4 h normocarbic hypoxia (FIO_2, 0.10). Intravenous ranitidine (1 mg/kg) did not modify the changes, although intravenous roxatidine (1 mg/kg) and famotidine (0.4 mg/kg) blunted the increase in CBF. Oxygen supply to the brain (CaO_2 mL O_2/mL blood × total CBF) decreased during hypoxia when roxatidine and famotidine were given. $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ versus control; NS, not significant.

than the change seen in the control group (Figure 1). Roxatidine equally blunted the increase of CBF in hypoxia in all the regions of the brain, and oxygen supply to the brain was decreased (Figure 1 and Table 3).

There was no difference in CBF between the ranitidine group and the control group. It is clear that ranitidine at 1 mg/kg did not prevent the modification of CBF during hypoxia because after 2 h there was a flow increase of 37%, and 26% after 4 h. These values do not differ statistically either among themselves or in relation to control group values. Studied by area, the increase in CBF was similar to that of the control group. Oxygen supply to the brain was maintained at a normal level during the two periods of hypoxia. However, the double-dose of ranitidine (2 mg/kg) completely blocked the increase in CBF during hypoxia in three additional dogs. Total CBF while breathing air was 70 ± 4 mL·min^{-1}·100 g^{-1}, and after 2 and 4 h of hypoxia 76 ± 4 and 72 ± 6 mL·min^{-1}·100 g^{-1}, respectively.

Discussion

The aim of this study was the evaluation of the effects on hypoxia-induced changes in CBF produced by ranitidine, famotidine, and roxatidine, all potent inhibitors of H_2-receptors.

In a previous study (6) we have shown that cimetidine blocks the increase in CBF normally observed during moderate hypoxia. In the present work, the same level of hypoxia (FIO_2, 0.10) was maintained for 4 h because a more profound hypoxia would have induced major hemodynamic alterations that could considerably influence CBF (12). To avoid the hemodynamic modifications due to anesthesia the animals were fully awake when studied.

Famotidine and roxatidine inhibited the hypoxia-induced increase in CBF, whereas the equipotent dose of ranitidine (1 mg/kg) did not affect this reaction. A double-dose (2 mg/kg) of ranitidine, tested in three dogs under the same conditions, demonstrated complete suppression of an increase in CBF during hypoxia.

As cerebral autoregulation is not maintained during hypoxia (13,14), these findings could have been the result of a decrease in blood pressure. In humans, intravenously injected cimetidine causes a transient decrease in mean arterial pressure due to a peripheral vasodilation, together with preservation of the cardiac output (15–17). Ranitidine has no such effects. Famotidine seems equally devoid of hypotensive action (16). These varying effects on systemic hemodynamics cannot account for the changes in CBF observed in our experiments because mean arterial pressure increases during hypoxia.

The effect of the H_2-blockers used in the present study on the H_2-receptors present in cerebral vessels and in the central nervous system could explain our observations. All H_2-blockers studied cross the blood-brain barrier (18–21), and three of them have similar cerebrospinal fluid/plasma ratios of concentration (18–20). Thus, brain penetration cannot account for the observed differences.

The possibility of a metabolic explanation can be invoked. Cimetidine is a powerful inhibitor of cytochrome P_{450}, the key enzyme in mitochondrial respiration (22). Cimetidine inhibits the cerebral mitochondrial respiration in rats (23). Ranitidine has a similar relationship with cytochrome P_{450}, but its affinity is 10 times less (24); this difference is due to the presence of a furane ring in place of the imidazole ring of cimetidine. The latter is also absent in the structure of famotidine, where it is replaced by a thiazole ring. On the contrary, famotidine and roxatidine do not block cytochrome P_{450} (25,26). Consequently, inhibition of cytochrome P_{450} cannot be given as an explanation because ranitidine, famotidine, and roxatidine would have the same effect. Nevertheless, the lack of effect of 1 mg/kg ranitidine is possibly linked to an insufficient dosage. The choice of the dose was made with regard to data in the literature on doses blocking gastric H_2-receptors. It is possible that cerebral H_2-receptors could have different sensitivities to H_2-blockers. For ranitidine the dosage had to be doubled to achieve the same effect.

The absence of an increase in CBF during hypoxia seen with blockade of H$_2$-receptors in cerebral vessels suggests that histamine acts as a vasoactive transmitter in hypoxia. A large number of mastocytes exist in the vicinity of the cerebral vessels (3), and the discharge of their histamine content is dependent on the H$_2$-receptors (27).

In conclusion, this study establishes differences in the actions of H$_2$-blockers on CBF during moderate hypoxia. When doses that are equipotent for gastric H$_2$-receptors were used, ranitidine allowed the increase in CBF induced by hypoxia to occur, whereas famotidine and roxatidine blocked it. When the dose of ranitidine was doubled, it also blocked the increase in CBF induced by hypoxia. These results should be kept in mind when prescribing anti-H$_2$ drugs in critically ill patients and in emergency anesthesia.

We are grateful to Francine Schrijen, Dominique Baptiste, Bernadette Clement, Ginette Hauquiert, and Marie-Claude Rohrer for their valuable help.

References

1. Kuschinsky W, Wahl M. Local chemical and neurogenic regulation of cerebral vascular resistance. Physiol Rev 1978;58:656–89.
2. Peroutka SJ, Moscowitz MA, Reinhard JR, Snyder JH. Neurotransmitter receptor binding in bovine cerebral microvessels. Science 1980;208:610–2.
3. Edvinsson L, Cervos-Navarro J, Larsson LL, Owman C, Ronnberg AL. Regional distribution of mast cells containing histamine, dopamine or 5 hydroxy-tryptamine in the mammalian brain. Neurology 1977;27:878–83.
4. Martins AN, Doyle TF, Wright SJ, Bass BG. Response of cerebral circulation to topical histamine. Stroke 1980;11:469–76.
5. Toda N. Mechanism underlying responses to histamine of isolated monkey and human cerebral arteries. Am J Physiol 1990;258:H311–7.
6. Clozel JP, Amend P, Saunier C, Hartemann D. Cimetidine inhibits the hypoxia-induced increase in cerebral blood flow in dogs. Crit Care Med 1985;13:976–81.
7. Daly MJ, Humphray JM, Stables R. Inhibition of gastric acid secretion in the dog by the H$_2$-receptor antagonists: ranitidine, cimetidine and metramide. Gut 1980;21:408–12.
8. Scarpignato C, Tramacere R, Zappia L. Antisecretory and antiulcer effect of the H$_2$-receptor antagonist famotidine in the rat: comparison with ranitidine. Br J Pharmacol 1987;92:153–9.
9. Sewing KF. Chemical and biologic differences between various H$_2$-receptor antagonists. Scand J Gastroenterol 1988;23(Suppl 146):73–7.
10. Von Ritter C, Hinder HW, Womack W, et al. Microsphere estimates of blood flow: methodological considerations. Am J Physiol 1988;254:G275–9.
11. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide labelled particles. Prog Cardiovasc Dis 1977;20:55–79.
12. Myers RE, Kopf GS, Mirvis DM. Hemodynamic response to profound hypoxia in intact rhesus monkeys. Stroke 1980;11:389–93.
13. Häggendal E, Johansson B. Effects of arterial carbon dioxide tension and oxygen saturation on cerebral blood flow autoregulation in dogs. Acta Physiol Scand 1966;66(Suppl 258):27–53.
14. Dora E. Effect of theophylline treatment on the functional hyperaemic and hypoxic responses of cerebrocortical microcirculation. Acta Physiol Hung 1986;68:183–97.
15. Coursin DB, Farin-Rusk C, Springman SR, Goelzer SL. Hemodynamic effects on intravenous cimetidine versus ranitidine in intensive care unit patients: a double blind prospective cross over study. Anesthesiology 1988;69:975–8.
16. Omote K, Namiki A, Sumita S, Takahashi T, Ujike Y, Hagiwara T. Comparative studies on hemodynamic effects of intravenous cimetidine, ranitidine and famotidine in intensive care unit patients. Jpn J Anesthesiol 1987;36:940–7.
17. Iberti TJ, Paluch TA, Helmer L, Murgolo VA, Benjamin E. The hemodynamic effects of intravenous cimetidine in intensive care unit patients: a double blind prospective study. Anesthesiology 1986;64:87–9.
18. Jonsson VA, Eriksson JE, Kagevi I, Norlander B, Bodemar G, Walan A. Cimetidine but not oxmetidine penetrates into the cerebrospinal fluid after a single intravenous dose. Br J Clin Pharmacol 1982;14:815–9.
19. Kagevi I, Wåhlby I. CSF concentration of ranitidine. Lancet 1985;i:164–5.
20. Kagevi I, Thorhallson E, Wåhlby I. CSF concentrations of famotidine. Br J Clin Pharmacol 1987;24:849–50.
21. Tryba M, Kurtz-Muller K. Penetration of roxatidine into the cerebrospinal fluid. Scand J Gastroenterol 1988;23(Suppl 146):153–8.
22. Bast A, Savenije-Chapel EM, Kroes BH. Inhibition of monooxygenase and oxidase activity of rat hepatic cytochrome P450 by H$_2$-receptor blockers. Xenobiotica 1984;14:399–408.
23. Ghersi-Egea JF, Sautegeau A, Walther B, Minn A, Saunier C. Cimetidine inhibits cerebral and hepatic mitochondrial respiration in rat. Toxicol Lett 1986;34:253–9.
24. Rendic S, Kajfez F, Ruf HM. Characterization of cimetidine, ranitidine and related structures interaction with cytochrome P450. Drug Metab Dispos 1983;11:137–42.
25. Somerville KW, Kitchingman GA, Langman MJJ. Effect of famotidine on oxidative drug metabolism. Eur J Clin Pharmacol 1986;30:279–81.
26. Scholtholt J, Bickel M, Herling AW. A review of the animal pharmacology of roxatidine acetate. Drugs 1988;35(Suppl 3):30–40.
27. Lichtenstein LM, Plaut M, Henney C, Gillespie E. The role of H$_2$-receptors on the cells involved in hypersensitivity reactions. In: Wood CJ, Simkins MA, eds. International symposium on histamine H$_2$-receptor antagonists. Welwyn, Garden City, U.K.: Smith Kline and French Laboratories Limited, 1973:187–98.

Historical Article

The Development of Academic Anesthesiology at the Roswell Park Memorial Institute: James O. Elam, MD, and Elwyn S. Brown, MD

James E. Peppriell, PhD, MD, Douglas R. Bacon, MD, Mark J. Lema, PhD, MD, Richard Ament, MD, and Clifton K. Yearley, PhD

PEPPRIELL JE, BACON DR, LEMA MJ, AMENT R, YEARLEY CK. The development of academic anesthesiology at the Roswell Park Memorial Institute: James O. Elam, MD, and Elwyn S. Brown, MD. Anesth Analg 1991;72:538–45.

In the early 1950s, Drs. James Elam and Elwyn Brown were recruited to establish the department of anesthesiology at the Roswell Park Memorial Institute. With substantial financial support from both the New York State coffers and the Institute's director, Dr. George Moore, Elam and Brown were able to create a department of anesthesiology renowned for clinical excellence and basic science research. Their work on carbon dioxide elimination led to a redesigning of the soda lime canisters that is still in clinical use. By popularizing mouth-to-mouth rescue breathing, these two anesthesiologists changed the manner in which emergency aid was given and won international acclaim.

Key Words: HISTORY, ELAM, BROWN, AND ROSWELL PARK MEMORIAL INSTITUTE. CARBON DIOXIDE, ABSORPTION—history. VENTILATION, ARTIFICIAL—history.

The emergence of a discrete medical specialty—academic anesthesiology—and the arrival of the Roswell Park Memorial Institute of Buffalo, New York, as one of the foremost cancer research centers occurred simultaneously. What had begun as a small state-supported hospital for the clinical study of cancer had, by the early 1950s, expanded to a world leader in both scientific research and clinical treatment of cancer. Triggered by an abundance of state funds and the drive and imagination of the Roswell Park Memorial Institute's youngest director, Dr. George Moore (Figure 1), the Institute grew exponentially. The creation of the first department of anesthesiology remains reflective of the monumental changes occurring in Buffalo's "Cancer Hospital."

Central to the development of the Roswell Park Memorial Institute and the establishment of its anesthesiology department were Drs. James O. Elam and Elwyn S. Brown (Figures 2 and 3). Leaving the Barnes Hospital in St. Louis, Missouri, in 1953, they ventured forth to Buffalo, eager to create a department of anesthesiology. Under the administration of the new director of the Institute, Dr. Moore, they were charged with the task of establishing excellence in clinical practice and of creating an atmosphere conducive to basic research. The successes of Elam and Brown ultimately surpassed anyone's expectations, winning both international acclaim and financial resources for the Institute through the patenting of their work.

Soon after their arrival in Buffalo, Elam and Brown set about the development of a physician-directed clinical department in anesthesiology where none had previously existed. Simultaneously, they continued the research in respiratory physiology they had begun at Barnes Hospital. A vigorous campaign to

---

Received from the Departments of Anesthesiology and History, State University of New York at Buffalo, New York. Accepted for publication November 26, 1990.

Address correspondence to Dr. Bacon, Department of Anesthesiology and Critical Care Medicine, Roswell Park Memorial Institute, Elm and Carlton Streets, Buffalo, NY 14263.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Figure 1. George Moore, MD (photograph courtesy of the Roswell Park Memorial Institute).

Figure 2. James O. Elam, MD (photograph courtesy of the Roswell Park Memorial Institute).

recruit anesthesiologists to fill the allocated staff positions was immediately launched. Elam and Brown also developed a school of nurse anesthesia to ensure that the number of clinical support staff would be adequate so that their research might continue without pause.

Research remained paramount, and soon after their arrival, they published the first in a series of

Figure 3. Elwyn S. Brown, MD (photograph courtesy of the University of Iowa).

classic articles on "rescue breathing." This work led to other areas of investigation, such as carbon dioxide absorption, artificial ventilation, and the circle system for anesthetic gas delivery. Their work was recognized nationally and internationally, yet within the Buffalo academic community they remained little known. Seeking greater educational opportunities, Elam and Brown left Buffalo after 12 years for new opportunities with greater academic exposure. Shortly after leaving western New York, they separated, each seeking new challenges in different cities.

The impact of the work of Elam and Brown at the Roswell Park Memorial Institute in one sense was easy to measure. Every anesthesia machine over the last 30 years has used a carbon dioxide absorbance system essentially designed by these two physicians. Elam and Brown clearly demonstrated the superiority of mouth-to-mouth resuscitation, and, later, mouth-to-mask resuscitation, over the conventional method of posterior chest compression. Their concepts ultimately transformed the international standards for cardiopulmonary resuscitation. However, much of the background behind this work remains unknown.

A Brief History of the Roswell Park Memorial Institute

In 1898 the New York State Pathologic Laboratory was established largely through the efforts of the politically prominent editor of the *Buffalo Evening News*, Edward H. Butler, Sr., and the internationally famous surgeon, Dr. Roswell Park. When Governor Frank S. Black refused their grant application in 1897, Butler and Park intensified their lobbying efforts to obtain, in 1898, $7500.00 from the state coffers. New York thus became the first state to subsidize cancer research (1).

During the Laboratory's first half-century, its mission was largely clinical, with an emphasis on the diagnosis and treatment of cancer, as well as on recording the natural history of the disease (2). Dr. Roswell Park was the Institute's first director, a position he retained for only 6 years. It is very important, however, that he remained on the Board of Governors until his death in 1914, to ensure fulfillment of the Laboratory's mission (3).

In 1946, 32 years after Park's death, the New York State Legislature renamed the Institute in his honor (4). With that change effected, others were contemplated. Dr. Louis Kress, the Institute's director in the early postwar period, constantly reminded Albany policy-makers of the deplorable conditions that had developed at the nation's oldest cancer hospital. Salaries were low, making it difficult to attract qualified personnel. Financial resources for books, supplies, and construction materials were delayed. Eventually, research slowed to a halt because of insufficient laboratory space for scientific work (5).

By 1949, Albany legislators, particularly Edwin Jaekel, Buffalo's powerful New York State Senate majority leader (6), had been persuaded by Kress' reports to initiate a major policy shift toward the Institute's improvement. The plans Jaekel and Kress developed were grand: a downtown Buffalo city block bounded by Oak, Carlton, Elm, and High Streets would house the new Roswell Park Memorial Institute. And, within those proposed bounds, "the most modern and one of the best equipped" cancer research hospitals would be built (7).

Actualization of the project began in 1951. Ground was broken on October 27 of that year and construction followed in March 1952 (8). Unfortunately, Kress died shortly thereafter, long before the new Institute was completed; fortunately, New York State's Commissioner of Health, Herman Hilliboe, had the foresight to understand that the new director must be a dynamic driving force if the Institute were to fulfill its mission. In November 1952 he appointed a young associate professor of surgery from the University of Minnesota, George Moore. At 32 years of age Moore was both the youngest Institute director and a visionary capable of bringing the Roswell Park Memorial Institute international acclaim in clinical and basic science research (9).

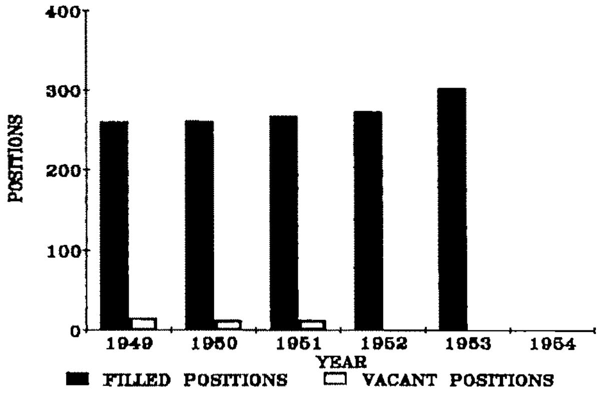


Figure 4. Number of staff positions (professional and nonprofessional) at the Roswell Park Memorial Institute.

Moore's plan was marked by its simplicity: attract bright, young physicians interested in research and scientific publication and assure them of one universally scarce item: RESEARCH SPACE. Moore's nonprofit corporation, Health Research, Inc., was created to perform the necessary service of maintaining an adequate cash flow for research funds (10).

Moore's impact on the clinical efforts of the Institute was manifested almost immediately. Staff positions greatly increased (Figure 4) during the year after his appointment. Filling chief of clinical service positions was his most notable accomplishment. The number of major surgical procedures would more than double while minor operations increased 20% within the first year of his appointment (11)!

Possibly of greater significance, scientific articles published by Institute personnel grew exponentially in number under Moore's guidance. His ability to attract productive, research-oriented staff is best reflected by the fact that the quantity of publications doubled in his first year at Roswell. By 1954, the number of papers published by Institute personnel in scientific journals rose to six times the level before Moore's arrival (12) (Figure 5).

On October 14, 1954, 3 years after ground breaking, a new 7-million-dollar addition to the Institute was dedicated, and Albany's dream of a comprehensive cancer center slowly developed into reality. Desirous of participating in such promising ventures, the University of Buffalo established a Roswell Park Division of its graduate school, with approval for initiation of masters' and doctoral degree programs the following year (13). The association marked a joining of private and state educational interests and acknowledged the "coming of age" of the Roswell Park Memorial Institute.

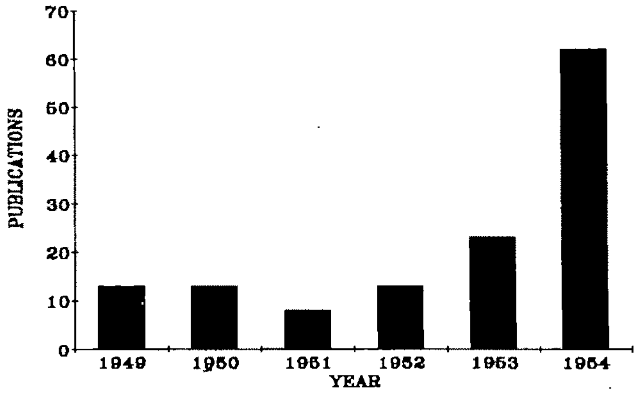


Figure 5. Number of publications at the Roswell Park Memorial Institute, 1949–54.

Formation of the Anesthesiology Department

The Roswell Park Memorial Institute Department of Anesthesiology was nonexistent before Moore's recruitment of James Elam in 1953 (14). At Barnes Hospital and Washington University where they had been previously affiliated, anesthesiology was a section of the department of surgery. Elam did not agree with the endeavor by the University's new chairman of surgery to reassign the anesthesiologists' research efforts from practical patient care to animal studies (15). Elam feared that his annual Army contract of $35,000 a year to study artificial respiration was in jeopardy and quickly accepted Moore's offer (16).

The invitation to Elam obviously involved structuring an academic anesthesiology department. In addition to a title, Moore proffered more than 60,000 sq ft in the main hospital building. Elam was given complete control over the operating room schedule along with sufficient salaries for himself and his staff, to which was appended a "generous personnel allowance" to aid in research efforts (17).

With the Institute undergoing a metamorphosis, Elam quickly realized that increasing demands would be placed on the fledgling anesthesia department. Surgical services and subspecialties were increasing in size and scope, and new departments were being created (18). To ensure the predominant influence of his newly created, physician-directed anesthesiology division, Elam astutely recruited two physicians, Elwyn Brown and Raymond Ten Pas, from the remaining disenchanted staff at Barnes Hospital in St. Louis. In addition, Elam was able to augment his clinical staff by recruiting two local anesthesiologists (19).

Yet, even with five physicians, the staff of the anesthesia service was still inadequate. Elam inherited two certified registered nurse anesthetists (CRNAs) and quickly hired a third. Due to a national shortage, however, Elam failed to recruit additional CRNAs for work at the Institute (20).

To circumvent this problem, Elam created a training program in anesthesia for nurses. Criteria for entrance were loose; the program solicited ward nurses expressing an interest in the field. Utilizing the services of his superb supervising CRNA, Miss Anne Seniff, as a supervisor, novitiate nurses spent weekdays in the operating room learning "hands on" anesthesia (21). Saturdays were devoted to seminars covering such topics as physiology, pharmacology, and anesthetic equipment, which were conducted by Elam and the other departmental physicians (22). Although the instruction was rigorous, all of the nurses in the first class completed their training and, by the end of the first year, were employed as nurse anesthetists (23).

Elam's direct amelioration of his difficulties was masterful. The school was now anchored within the confines of his department, and he was confident of having a steady supply of anesthesia personnel to cover the clinical responsibilities. His flanks covered, Elam was then free to expand his department's research mission.

Carbon Dioxide Investigations

Elam, Brown, and Ten Pas arrived in Buffalo with two trailers filled with research equipment from their laboratory in St. Louis (24). Their Buffalo colleagues were impressed. As one remarked, "None of us had ever seen such equipment before, and could not imagine it had anything to do with anesthesia" (25). Packed somewhere within the trailers was a new Liston-Becker model 16 carbon dioxide analyzer, which measured carbon dioxide concentrations by infrared spectral analysis (26). Simple to use, the instrument required calibration with a known concentration of carbon dioxide (27).

The analyzer was used to evaluate an old anesthetic problem: carbon dioxide elimination from closed-circuit systems. Introduced in 1930 by Brian Sword, a New Haven, Connecticut, anesthesiologist, the closed circuit reduced the amount of fresh anesthetic gas needed to anesthetize a patient properly (28), thereby reducing the cost of anesthesia for expensive gases like cyclopropane (29). However, prolonged use of the closed-circuit system, regardless of the agent employed, resulted in hypertension, tachycardia, diaphoresis, ventricular fibrillation, and even death (30).

Work on this problem was urgently needed. While several investigators, including Dr. John Adriani (at that time an anesthesiologist at Bellevue Hospital), had attempted to clarify and resolve the situation in the late 1930s and early 1940s, their calculations involved tedious and error-prone stoichiometric titrations (31). A simple system capable of reliably removing carbon dioxide was desperately needed. Pioneer anesthesiologist and University of Wisconsin chairman Ralph Waters observed in 1947 (32) that

> If modern chemists and engineers can construct a warship which can safely and comfortably carry a large number of men for days and weeks at or near the bottom of the ocean, they *should* be able to help us construct an anesthetic apparatus of small bulk and cost which can "keep pure" indefinitely, the atmosphere respired by a single patient.

Elam, Brown, and Ten Pas vigorously accepted Waters' challenge. Still supported by their Army contract, they produced the first published capnographic profile of human respiration in the anesthesiology literature by applying the Liston-Becker analyzer to a volunteer's expired breath. Although the bulk of the research had been completed before their departure from St. Louis, publication occurred in four parts after their arrival in Buffalo in the journal *Anesthesiology* (33–36).

Several reasons accounted for the series' significance. In the first paper, the "alveolar plateau" of carbon dioxide in expired breath was delineated. Once this reproducible, normal wave form was clearly defined, application to altered states of respiration became possible. Both hyper- and hypoventilation posed problems for uptake and distribution of anesthetic agents. More important, the analyzer also detected inspired carbon dioxide concentrations that helped identify the source of altered anesthetic uptake. The "abnormal" states were often due to equipment failure, operator failure, incomplete carbon dioxide absorbance by soda lime, incompetence of the anesthetic circuit valves, or inadequate lung inflation (33). Elam and Brown had discovered a method to diagnose insufficient ventilation during general anesthesia. Years later the same principles would be applied so that the end-tidal carbon dioxide monitor would become the "standard of care" in anesthetic practice.

The second and third papers of the series dealt with more esoteric aspects of respiratory physiology. Using their new technology, Elam and Brown were able to determine a patient's dead space, anesthetic mask dead space, alveolar ventilation, and carbon dioxide output on a breath-by-breath basis (34). They vividly demonstrated the interaction between ventilation and carbon dioxide elimination, a problem that had plagued anesthesiologists for decades (35).

Controversy erupted around the final segment in the series. In this manuscript, Elam and Brown, with aid of the analyzer, demonstrated that the conventional flow rate of less than 10 L/min of "fresh" gas, in semiclosed systems, caused continuous elevations in inspired carbon dioxide concentrations, thus refuting contemporary conventional wisdom. Their paper concluded: "Inflow rates of fifteen LPM [L/min] are not sufficient to prevent accumulation of carbon dioxide in all patients, and the commonly used inflow rate of ten LPM may result in concentrations above four per cent inspired carbon dioxide in spite of excessive hyperventilation" (36).

Elimination of inspired carbon dioxide from semiclosed anesthetic breathing circuits was a persistent challenge that intrigued Elam and Brown. Realizing the futility of simply increasing the fresh gas flows from both a practical and monetary perspective, they began to experiment with soda lime. Building on the work of Adriani (37), they discovered that the interstitial space within the canister should closely approximate tidal volume (38). Absorption of carbon dioxide was maximally efficient when the soda lime contained 20%–25% water (39). It was discovered that channeling, a phenomenon in which expired gas flowed directly through the canister, bypassing interaction with the lime, depended on how the granules were packed. Finally, the use of baffles to redirect gas flow kept channeling to a minimum (40). Longer lasting carbon dioxide absorption was, for the first time, clinically available through their redesigned dual soda lime canisters (41).

Their soda lime studies, however, were contingent on the development of a lung analogue that would accurately and reproducibly simulate a respiring human. The investigators' first working ventilator model was somewhat impractical. The bulk of their apparatus (a motor, variable speed reducer, cam shaft, piston, rate control, thermostated heater, piston-driven bellows, multiple inspiratory and expiratory valves, tubing for gas infusion, and the canister itself with the Liston-Becker analyzer interposed in the dead space) made research difficult (42). Despite its size, the system functioned as designed for well over 5 years, providing data 24 hours a day. Different carbon dioxide canister models and breathing circuit resistances were tested. The model helped evaluate methods for estimation of both anatomic and physiologic dead space. Elam and Brown realized that the equipment could simulate different human respiratory patterns by simply changing cams and rate controls. If it were possible to construct a machine that could breathe *like* a patient, Elam and Brown reasoned that it should be possible to construct a machine to breathe *for* a patient. The redesigning of the cam arm, and a windshield-wiper motor manufactured by the Buffalo-based Trico Industries, led to the successful conversion of their idea into practice. It was an amazing invention, for the respirator could cycle in a positive-negative, positive-zero, and positive pressure manner. Uniquely, the unit functioned in either a pressure or volume mode. Using the model on their analogue system first, and then on humans, the machine provided adequate carbon dioxide homeostasis (43) and was christened the Roswell Park Ventilator (44). With some modifications this ventilator continues in use as the Air-Shields Ventimeter.

Rescue Breathing

Of all the contributions James Elam and Elwyn Brown gave to the medical community, one series of papers provoked repercussions at home and abroad. Disaster, of course, underlay their achievements. Elam's first encounter with rescue breathing was mouth-to-endotracheal respiration for patients during the Minnesota poliomyelitis epidemic of 1946 (45). Brown was introduced to the idea by Visiting Professor of Anesthesia Trier Morch from the University of Chicago during his residency in St. Louis in 1950. Unable to stimulate respiration in an intubated patient in the recovery room, the expert's advice was simple: "blow into the tube" (46).

Applying the Liston-Becker Analyzer and Van Slike blood gas analysis to the problem, Elam and Brown had demonstrated at Barnes Hospital that mouth-to-mask respiration could maintain normal gas exchange in patients reparalyzed in the recovery room by an infusion of succinylcholine. Although the demonstration was initially approved by Dr. Graham, the outgoing chairman of surgery at Barnes Hospital, condemnation came quickly from his replacement who stoutly insisted that the work continue solely on animal models. Because the investigators could not design a mask fitting a dog and because such a change in course would have jeopardized their Army contract, they left St. Louis for the Roswell Park Memorial Institute ready to pursue their original line of inquiry (47).

Shortly after their arrival, Elam and Brown's initial study was published in the *New England Journal of Medicine* (48). Sustaining their studies, Elam and Brown—along with numerous international collaborators—demonstrated that airway patency was critical for successful rescue breathing. A simple extension of the neck and anterior displacement of the mandible was usually sufficient to secure a patent airway. The older, more cumbersome chest pressure arm-lift methods of artificial respiration were ineffective because, with or without a patent airway, insufficient tidal volumes to sustain life would be delivered to the patient's lungs (49).

The simplicity of the technique of Elam and Brown impressed New York Health Commissioner Hilliboe, who requested that Elam and Brown prepare an instructional booklet entitled *Rescue Breathing* for national distribution in 1959 (50).

Furthermore, employing more popular media to promulgate their discovery, Elam and Brown produced films aimed at both professional audiences and the general public to demonstrate their techniques (51). With support from the U.S. Army, which controlled distribution, the films sold for $38 each. Lent out on free loan, these educational movies were often not returned (52). Elam's popularity as a speaker soared because his lectures were often accompanied by one of his films (53).

By 1960, Elam and Brown's recommended method of artificial respiration was adopted by the National Academy of Sciences, the American Society of Anesthesiologists, the Medical Society of the State of New York, and the American Red Cross as the method of rescue breathing. The U.S. Army also recognized Elam's accomplishments by awarding him a Certificate of Achievement, and in 1962 the Medical Society of the State of New York, following suit, bestowed upon Elam the prestigious Albion O. Bernstein Award.

Conclusions

For 11 years, the anesthesiology department at the Roswell Park Memorial Institute led the nation, perhaps the world, in carbon dioxide research. Not only encouraged by George Moore, but also funded for 14 years by a $35,000 yearly Armed Forces contract (the equivalent of about $500,000 today), Elam and Brown fully availed themselves of their opportunities. In that short time-span, they contributed over 50 articles to prestigious journals including *Anesthesia and Analgesia, Anesthesiology, The New England Journal of Medicine, The Journal of the American Medical Association, Annals of the New York Academy of Sciences,* and the *Journal of Applied Physiology.*

The magic formula that made their work possible, in retrospect, was quite simple. Elam possessed a charismatic and determined personality, and Brown was a mechanical engineer by training. While Jim Elam dreamed and schemed, Elwyn Brown pragmatically brought the dreams and schemes to fruition. Coupled with abundant financial and personnel support and a "more relaxed" attitude toward medical research protocols and informed consent, they created an atmosphere in which serious research could be pursued.

Yet, as may happen with many good things, the department folded. Elam hoped the younger generation would disseminate word of his accomplishments, yet sadly he had no residents. Three established anesthesia programs trained housestaff in Buffalo at the time, but residents from these programs did not rotate through the Roswell operating rooms and so were never exposed, first-hand, to Elam's work or personality. Lacking the necessary obstetric and pediatric rotations and a sufficient case load to establish their own program (54), Elam and Brown sought in 1964 greener pastures at the University of Kansas Medical Center. Elam was appointed professor and chairman of the Department of Anesthesiology. Brown left shortly after their arrival to pursue his interests in pulmonary surfactant and pediatrics. Elam also left the University of Kansas after a few years. He has remained interested in artificial ventilation and rescue breathing even after ending his clinical career in Chicago in the mid-1980s.

During their Roswell Park Memorial Institute tenure, Elam and Brown converted a part-time consultant anesthesia service into an internationally regarded anesthesiology department. Their work in carbon dioxide homeostasis and absorption, mechanical ventilation, and artificial respiration can best be classified as both innovative and ingenious. Perhaps Paterno C. Albano, acting chief of the Department of Anesthesiology on Elam's departure, accurately described their contribution in the first annual report written the year after their departure: "The research program . . . has suffered considerably with the wholesale exodus of clinical and scientific staff" (55). Without question, their absence was acutely felt at Roswell Park. However, as a testimony to the import of their work, Elam and Brown's research remains a standard by which all academic anesthesiologists may be judged.

References

1. Spencer M. Major cancer research center began 75 years ago. The Buffalo Sunday News, June 23, 1973, p. B-3.
2. Moore GE, Roswell Park Institute, hope for millions. Buffalo Business, April 1956, p. 3.
3. Mirand EA. The history of the Roswell Park Memorial Institute. Niagara Frontier 1961;8:61.
4. Annual Report of the Roswell Park Institute, 1946, p. 11.
5. Annual Report of the Roswell Park Memorial Institute, 1951, pp. 10–20.
6. Personal communication, Richard Ament, MD.
7. Annual Report of the Roswell Park Memorial Institute, 1949, p. 12.
8. Annual Report of the Roswell Park Memorial Institute, 1951, pp. 10–20.
9. Spencer M. Major cancer research center began 75 years ago. The Buffalo Sunday News, June 23, 1973, p. B-4.
10. Annual Report of the Roswell Park Memorial Institute, 1953, p. 12.
11. Annual Report of the Roswell Park Memorial Institute, 1949–54.
12. Annual Report of the Roswell Park Memorial Institute, 1952–54.
13. Mirand EA. The history of the Roswell Park Memorial Institute. Niagara Frontier 1961;8:66.
14. Personal communication, George E. Moore, MD, PhD.
15. Personal communication, Elwyn S. Brown, MD.
16. Personal communication, James O. Elam, MD.
17. Personal communication, James O. Elam, MD.
18. Annual Report of the Roswell Park Memorial Institute, 1953, p. 14.
19. Annual Report of the Roswell Park Memorial Institute, 1953, p. 81.
20. Annual Report of the Roswell Park Memorial Institute, 1953, p. 82.
21. Personal communication, Anne Seniff, CRNA.
22. Personal communication, James O. Elam, MD
23. Annual Report of the Roswell Park Memorial Institute, 1954, p. 72.
24. Personal communication, Elwyn S. Brown, MD.
25. Personal communication, Richard N. Terry, MD
26. Flower RC. Rapid infrared gas analyzer. Rev Sci Instrum 1949;20:175.
27. Luft K. Methode der registrieren gas Analyse mit Hilfe der Absorption ultraroten Strahlen ohne spectrale Zerlegung. Z Tech Phys 1943;24:97.
28. Sword BC. The closed circle method of administration of gas anesthesia. Curr Res Anesth Analg 1930;9:198.
29. Waters RM, Schmidt ER. Cyclopropane anesthesia. JAMA 1934;103:975.
30. Brown EB, Miller F. Ventricular fibrillation following a rapid fall in alveolar carbon dioxide concentration. Am J Phys 1952;169:56.
31. Adriani J, Rovenstein EA. Experimental studies on carbon dioxide absorption for anesthesia. Anesthesiology 1941;2:1.
32. Waters RM. Absorption of carbon dioxide from anesthetic atmospheres: historical artifact. Anesthesiology 1947;8:339.
33. Elam JO, Brown ES, Ten Pas RH. Carbon dioxide homeostasis during anesthesia I. Instrumentation. Anesthesiology 1955;16:876.
34. Elam JO, Brown ES. Carbon dioxide homeostasis during anesthesia. II. Total sampling for determination of dead space, alveolar ventilation, and carbon dioxide output. Anesthesiology 1955;16:886.
35. Elam JO, Brown ES. Carbon dioxide homeostasis during anesthesia. III. Ventilation and carbon dioxide elimination. Anesthesiology 1956;17:116.

36. Elam JO, Brown ES. Carbon dioxide homeostasis during anesthesia. IV. An evaluation of the partial rebreathing system. Anesthesiology 1956;17:129.
37. Adriani J, Rovenstein EA. Experimental studies on carbon dioxide absorption for anesthesia. Anesthesiology 1941;2:1.
38. Brown ES. Factors affecting the performance of absorbants. Anesthesiology 1959;20:198.
39. Brown ES, Bakamjian V, Seniff AM. Performance of absorbants: effects of moisture. Anesthesiology 1959;20:613.
40. Elam JO. Channeling and overpacking in carbon dioxide absorbers. Anesthesiology 1958;19:403.
41. Brown ES, Senniff AM, Elam JO. Carbon dioxide elimination in semiclosed systems. Anesthesiology 1964;25:31.
42. Elam JO, Brown ES, Elder JD. A mechanical ventilator analog. Unnumbered report, USAF School of Aviation Medicine, Randolf Field, Texas, May 1954.
43. Elam JO, Brown ES, Janney CS. Ventilator. Anesthesiology 1956;17:504–17.
44. Personal communication, James O. Elam, MD.
45. Jude JA. Origins and evolvement of cardiopulmonary resuscitation. In: Atkinson RS, Boulton TB, eds. The history of anaesthesia. New York: The Parthenon Publishing Group, 1989:452.
46. Personal communication, Elwyn S. Brown, MD.
47. Personal communication, James O. Elam, MD, and Elwyn S. Brown, MD.
48. Elam JO, Brown ES, Elder JD. Artificial respiration by mouth to mask method, a study of the respiratory gas exchange of paralyzed patients ventilated by operator's expired air. N Engl J Med 1954;250:1954.
49. Elam JO, Greene DG, Brown ES, Clements JA. Oxygen and carbon dioxide exchange and the energy cost of expired air resuscitation. JAMA 1958;167:328.
50. Rescue breathing: Albany, N.Y.: New York State Department of Health, Health Education Services, N.Y.
51. Personal communication, P. S. Klein.
52. Personal communication, H. E. Dixon.
53. Letter from James O. Elam to Paul M. Wood, July 14, 1959. In: The collected papers of Paul M. Wood, M.D. The Collection of the Wood Library Museum of Anesthesiology, Park Ridge, Ill.
54. Personal communication, John I. Lauria, MD.
55. Annual Report of the Roswell Park Memorial Institute, 1964, p. 72.

546 ANESTH ANALG
1991;72:546–8

Clinical Reports

Plasma Concentration of Bupivacaine After Stellate Ganglion Blockade

Hinnerk Wulf, MD, Christoph Maier, MD, Hans-Albrecht Schele, MD, and Wolfgang Wabbel, MD

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—stellate ganglion block. ANESTHETICS, LOCAL—bupivacaine.

Stellate ganglion blockade is a well-established method for management of certain chronic pain syndromes of the cervicothoracic region and upper extremity. With repeated blocks, permanent relief of pain is often obtained. However, the incidence of side effects arising with stellate ganglion blockade is comparatively high (1). Although severe complications are rare, they can be life-threatening and can occur even in the hands of experts. Because of the high vascularity of cervical tissues, rapid absorption of the local anesthetic and, consequently, high plasma concentrations may occur. This has, however, never been quantified, to the best of our knowledge. We therefore undertook a study to determine the plasma concentrations of bupivacaine after stellate ganglion blockade.

Patients and Methods

After written informed consent and approval by our ethics committee, 11 consecutive patients in our pain clinic scheduled for a series of stellate ganglion blockades were investigated. The clinical data and pain syndromes of these patients are summarized in Table 1. Stellate ganglion blockade was performed with 10 mL of 0.5% bupivacaine using the paratracheal anterior technique with the needle aimed at the transverse process of C-6 (2). Repeated aspiration was done during performance of the block with the needle rotated between each attempt. These tests were done after each 2 mL of solution had been injected, about 60 s being required for injection of the entire 10 mL. Heart rate, arterial pressure, and side effects were recorded. Peripheral venous blood samples (3 mL) were drawn from the forearm of the contralateral side for determining plasma concentrations of bupivacaine 5 and 10 min before injection and 2, 5, 10, 15, 20, 30, 45, and 60 min thereafter.

The plasma concentrations of bupivacaine were measured as described previously (3). In short, plasma samples were assayed in duplicate by reversed-phase high-performance liquid chromatography with ultraviolet detection. Bupivacaine was extracted from plasma by solid-phase extraction. The recovery from the extraction procedure was 98.5%. Propranolol was used as an internal standard. The coefficient of variation showed acceptable precision of the assay in the range of 0.02–10 mg/L (5.3%).

Results

Clinical Results

Ipsilateral Horner's syndrome developed in all but one patient (patient 2). Nevertheless, a remarkable increase in skin temperature occurred in this patient. With the exception of patient 7 all patients had significant pain relief lasting at least 6 h. Three patients (1, 5, and 11) developed a temporary partial brachial plexus blockade after the injection. In two

---

Received from the Department of Anesthesiology, University Hospital of Kiel, Kiel, Germany. Accepted for publication November 14, 1990.

Address correspondence to Dr. Wulf, Department of Anesthesiology, University Hospital of Kiel, Schwanenweg 21, D 2300 Kiel, Germany.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

Table 1. Biometrical Data and Clinical Diagnoses

Patient No.	Sex	Age (yr)	Body weight (kg)	Pain syndrome
1	F	28	65	Atypical facial pain
2	F	33	97	Raynaud's syndrome
3	F	32	68	Sympathetic reflex dystrophy
4	F	63	73	Atypical facial pain
5	M	31	74	Atypical facial pain
6	M	66	72	Postherpetic neuralgia
7	M	75	61	Brachialgia as a result of radiation myelopathy
8	F	53	62	Lesion of brachial plexus after radiation
9	M	63	46	Raynaud's syndrome
10	M	47	77	Causalgia left arm
11	F	50	49	Causalgia left arm

women (patients 3 and 8) signs of central nervous system toxicity occurred. Patient 3 reported dizziness and buzzing in the ears that started immediately after injection of bupivacaine and lasted 3 min; no further symptoms developed. Patient 8 developed a generalized seizure during the injection. Aspiration tests before the injection started and after the injection of 2 mL had been negative. After administration of 20 mg bupivacaine (4 mL) this patient developed a generalized seizure. The injection was immediately stopped and the needle withdrawn. Instantly, oxygen was given by a face mask and 5 mg midazolam was administered intravenously. Within 3 min she regained consciousness. After 5 min she had a Horner's syndrome and pain relief in her arm lasting approximately 18 h. She was discharged from the hospital 3 h later without further sequelae.

No significant changes in heart rate or blood pressure were observed after the injection (always less than 15% deviation from baseline values) except in the patient with seizure.

Laboratory Findings

The median peak plasma concentration of bupivacaine after the injection of 50 mg of the substance for stellate ganglion blockade was 0.9 μg/mL. The median time to reach maximum values was 5 min. There was a remarkable interindividual variation in regard to C_{max} (range, 0.8–3.2 μg/mL) and t_{max} (range, 2–15 min) (Table 2). Three patients had maximum concentrations exceeding 2 μg/mL.

Discussion

The cervical region is a highly vascularized area. Therefore, rapid absorption or inadvertent intravascular injection of local anesthetics and, consequently, high and presumably toxic plasma concentrations may be assumed. Nevertheless, plasma concentrations of bupivacaine or any other local anesthetic after injection for stellate ganglion blockade are missing. The present study shows that the above assumption of rapid absorption is true. Despite interindividual variations, one can conclude that the absorption of bupivacaine is probably more rapid than with many other nerve blocks. In comparison, most authors have reported times to peak concentrations of bupivacaine in plasma to be 5–20 min after intercostal nerve block and 15–30 min after epidural blockade or brachial plexus block (4). Indeed, immediately after the injection of local anesthetics, arterial and central venous plasma concentrations might have been even higher than those determined in peripheral venous samples (5,6). But, from an ethical point of view, it was not regarded as appropriate to put arterial or central venous lines in patients in the present study.

In 3 of 11 patients, maximum venous plasma concentrations exceeding the threshold for central nervous system toxicity of approximately 2 μg/mL (7) were observed despite a comparatively low dose of 50 mg bupivacaine. In one of these patients, mild clinical symptoms of central nervous system toxicity developed (Table 2, patient 3). The most serious complication was a generalized seizure after the administration of only 20 mg bupivacaine. At the time of the seizure, the patient had rather low plasma concentrations of bupivacaine (Table 2, patient 8). Despite multiple negative aspiration tests, an inadvertent injection into the vertebral artery is the most probable explanation for this complication. All air was removed from the needle and syringe before the blockade. Thus, air embolism was not the cause of seizure; the local anesthetic itself was. Because the patient had a Horner's syndrome after the injection, only a part of the 20-mg dose must have been injected intraarterially; the rest must have reached the cervical sympathetic chain. This scenario is in accordance with the results reported in the literature showing that even smaller doses than 20 mg may result in such complications during stellate ganglion blocks. Korevaar and coworkers (8), as well as Kozody and coworkers (9), have reported on convulsions after 7.5 and 2.5 mg of bupivacaine. The estimated minimum toxic dose injected into a vertebral artery as a bolus can be derived from the following calculation (8,9): 15% of the cardiac output goes to the brain, and 20% of the total cerebral blood flow is through one of the vertebral arteries. If the injection is made rapidly into a vertebral artery, the minimum toxic dose will be 3%

Table 2. Plasma Concentrations of Bupivacaine (μg/mL) Before and After Stellate Ganglion Blockade With 50 mg of 0.5% Bupivacaine

	Time (min)									
Patient No.	−10	−5	+2	+5	−10	+15	+20	+30	+45	+60
1	0	0	1.3	1.3	1.0	1.0	0.9	0.8	0.5	0.4
2	0	0	2.2	1.2	0.8	0.4	0.4	0.3	0.2	0.2
3	0	0	3.2	2.5	0.8	0.8	0.7	0.4	0.4	0.4
4	0	0	0.8	0.9	0.8	0.5	0.5	0.5	0.3	0.3
5	0	0	0.3	0.7	0.8	0.8	0.7	0.6	0.4	0.4
6	0	0	0.4	0.8	0.8	0.8	0.6	0.6	0.5	0.3
7	0	0	0.3	0.4	0.6	0.8	0.7	0.7	0.7	0.6
8[a]	0	0	0.2	0.6	0.6	0.4	0.4	0.4	0.3	0.3
9	0	0	1.7	2.1	1.9	1.8	1.2	1.1	1.1	0.9
10	0.05	0.05	0.6	0.8	0.8	0.5	0.5	0.4	0.4	0.3
11	0	0	0.7	0.9	0.8	0.8	0.6	0.5	0.5	0.4

[a] The injection of bupivacaine was abandoned in this patient after application of 20 mg because of generalized seizure, most probably because of an inadvertent intraarterial injection.

of the minimum toxic intravenous dose (1.6 mg/kg), i.e., approximately 3.0 mg in a 62-kg patient (e.g., patient 8). Therefore, even a test dose smaller than 1 mL of 0.5% bupivacaine may result in convulsions if an inadvertent intraarterial injection occurs.

Several case reports of severe complications following stellate ganglion blockade have been published (8–12), but the true incidence remains to be evaluated. During the last 4 yr more than 600 stellate ganglion blockades with bupivacaine have been performed in our pain clinic. Three notable complications (1 in 200) occurred: an inadvertent subarachnoid injection (the patient was sedated and in need of artificial ventilation for 8 h without further sequelae), one generalized seizure (included in this study), and a marked bradycardia and syncope (probably a vagal reflex) not requiring specific treatment. The plasma concentrations reported in the present study, as well as the observed complications, emphasize the importance of the following recommendations:

1. Every patient scheduled for stellate ganglion blockade must have an intravenous line in place and must be monitored appropriately after the injection.
2. Resuscitation equipment must be readily available.
3. The person performing stellate ganglion blockade must be familiar with cardiopulmonary resuscitation and the treatment of possible life-threatening complications.
4. These blocks should be performed only when an assistant is present.
5. Even multiple aspiration tests do not exclude intraarterial injection. Therefore, all air should be removed from needles and syringes and a very small dose of local anesthetic should be used as a test dose.

References

1. Harding SP, Lipton JR, Wells JCD, Campbell JA. Relief of acute pain in herpes zoster ophthalmicus by stellate ganglion block. Br Med J 1986;292:1428.
2. Löfström JB, Cousins MJ. Sympathetic neural blockade of upper and lower extremity. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade. 2nd ed. Philadelphia: JB Lippincott, 1987:461–500.
3. Wulf H, Winckler K, Maier Ch, Heinzow B. Pharmacokinetics and protein binding of bupivacaine in postoperative epidural analgesia. Acta Anaesthesiol Scand 1988;32:530–4.
4. Tucker GT, Mather LE. Properties, absorption, and disposition of local anesthetic agents. In: Cousins MJ, Bridenbaugh PO, eds. Neural blockade. 2nd ed. Philadelphia: JB Lippincott, 1987:47–110.
5. Moore DC, Mather LE, Bridenbaugh PO, et al. Arterial and venous plasma levels of bupivacaine following epidural and intercostal nerve blocks. Anesthesiology 1976;45:39–45.
6. Bachmann B, Biscoping J, Adams HA, Menges T, Krumholz W, Hempelmann G. Die Bedeutung des Entnahmeortes bei der Bestimmung von Lokalanaesthetikakonzentrationen im Plasma am Beispiel von Bupivacain 0.75%. Reg Anaesth 1990; 13:16–20.
7. Jorfeldt L, Loefstroem B, Pernow B, Persson B, Wahren J, Widman B. The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand 1968;12:153–69.
8. Korevaar WC, Burney RG, Moore PA. Convulsions during stellate ganglion block: a case report. Anesth Analg 1979;58:329–30.
9. Kozody R, Ready LB, Barsa JE, Murphy TM. Dose requirement of local anesthetic to produce grand mal seizure during stellate ganglion block. Can Anaesth Soc J 1982;29:489–91.
10. Dhuner KG. Clinical experience with Marcaine (lac-43), a new local anaesthetic. Acta Anaesthesiol Scand 1966;10(Suppl 23): 395–401.
11. Szeinfeld M, Laurenico M, Pallares VS. Total reversible blindness following attempted stellate ganglion block. Anesth Analg 1981;60:689–90.
12. Colding A. The effect of regional sympathetic blocks in the treatment of herpes zoster. Acta Anaesthesiol Scand 1969;13: 133–41.

ANESTH ANALG 1991;72:549–51

Respiratory Failure Associated With Amnioinfusion During Labor

Debbie A. Dragich MD, Alan F. Ross, MD, David H. Chestnut, MD, and Katharine Wenstrom, MD

Key Words: ANESTHESIA, OBSTETRIC—amnioinfusion.

Saline amnioinfusion is a method to enlarge the amniotic cavity to relieve umbilical cord compression responsible for variable decelerations in fetal heart rate (1–4). Recently, amnioinfusion has been performed to dilute thick meconium to reduce the deleterious effects of fetal meconium aspiration (5,6). To our knowledge, there is no published report of a serious complication during amnioinfusion. We report the case of a patient who experienced acute respiratory failure during saline amnioinfusion.

Case Report

A healthy 24-yr-old woman, gravida 4, para 0, presented at 40.5 wk gestation in early labor. She had no history of cardiovascular or pulmonary disease and was a nonsmoker. Her pregnancy was complicated by fetal gastroschisis diagnosed at 19 wk gestation by ultrasound.

On admission the patient's vital signs were within normal limits. Fetal heart rate (measured by Doppler ultrasound) was 170–175 beats/min with little variability. Contractions were occurring every 2–4 min. Intravenous hydration and administration of supplemental oxygen (4 L/min by nasal cannula) were begun.

One hour and ten minutes after admission the patient vomited once. She remained alert and had no coughing or wheezing. Examination 15 min later revealed 1–2-cm cervical dilation with 80% effacement. Fetal heart rate was 170–180 beats/min with decreased variability. Amniotomy was performed and revealed amniotic fluid containing thick meconium. A fetal scalp electrocardiogram lead and intrauterine pressure catheter were placed. Amnioinfusion of 500 mL normal saline via the intrauterine pressure catheter was begun with an infusion pump at a rate of 999 mL/h. Fetal heart rate decreased to 160–170 beats/min during the amnioinfusion, but the decreased variability persisted. A second 500-mL amnioinfusion was administered, but the fetal heart rate remained at 160–170 beats/min with decreased variability.

Three hours after completion of the second amnioinfusion, the patient requested analgesia. Her cervix was 5 cm dilated and completely effaced. Fetal heart rate was 150–160 beats/min with variable decelerations to a rate of 80–90 beats/min with each contraction. Nalbuphine, 10 mg, was given intravenously. The patient continued to experience pain, and she requested epidural analgesia. Automatic blood pressure and electrocardiogram monitoring were begun. Lactated Ringer's solution, 900 mL, was infused intravenously over 30 min, and an epidural catheter was placed without difficulty via the L3-4 interspace. A test dose of 3 mL of 1.5% lidocaine with epinephrine 1:200,000 was given without evidence of intravenous or subarachnoid injection. At this time, a third 500-mL saline amnioinfusion was begun at 999 mL/h for treatment of variable decelerations.

Ten milliliters of 0.25% bupivacaine was injected epidurally over 10 min. A sensory level of T-11 was obtained, and the patient reported good pain relief. Blood pressure was 142/72 mm Hg, and maternal heart rate was 102 beats/min after analgesia was achieved.

Approximately 30 min after injection of the bupivacaine and near the completion of the third amnioinfusion, the patient became acutely dyspneic. Sitting upright with a respiratory rate of 32 breaths/min, blood pressure of 130/64 mm Hg, and heart rate of 128 beats/min, she had a cough that produced a clear, frothy yellow fluid. Rales were present diffusely over both lower lung fields, but wheezing was absent. (She had received 2 L of intravenous lactated Ringer's solution during the 7 h preceding the onset of dys-

---

Received from the Departments of Anesthesia and Obstetrics and Gynecology, University of Iowa College of Medicine, Iowa City, Iowa.

Address correspondence to Dr. Ross, Department of Anesthesia, University of Iowa College of Medicine, Iowa City, IA 52242.

Accepted for publication November 26, 1990.

Reprints will not be available from the authors.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

pnea.) With administration of oxygen, 2 L/min by nasal cannula, an arterial blood sample demonstrated a pH of 7.29, P_{CO_2} of 34 mm Hg, P_{O_2} of 74 mm Hg, bicarbonate of 15 mEq/L, and base deficit of −10 mEq/L.

At this time, while preparing to insert a urethral catheter, we noticed that the perineum was bulging, and the patient was transferred to the delivery room. Oxygen, 10 L/min, was administered by anesthesia face mask with a semiclosed circle system. Arterial oxygen saturation measured by pulse oximetry was maintained at 99%–100%. The respiratory rate was 38 breaths/min, blood pressure was 130/62 mm Hg, and heart rate was 124 beats/min. Twenty minutes after arrival in the delivery room, a 3360-g female infant with gastroschisis was delivered by low forceps over a midline episiotomy. Apgar scores were 2 and 6 at 1 and 5 min, respectively. Umbilical vein and artery pH values were 7.126 and 7.077, respectively. There was no evidence of uterine atony or excessive bleeding.

The patient continued to produce a copious clear yellow sputum that had a frothy appearance. A urethral catheter and a radial arterial catheter were placed. With administration of 100% oxygen by face mask, blood gas analysis demonstrated a pH of 7.23, P_{CO_2} of 39 mm Hg, P_{O_2} of 295 mm Hg, and a base deficit of −10 mEq/L. Intravenous administration of furosemide and nitroglycerin failed to improve the patient's symptoms.

A chest x-ray showed pulmonary vascular congestion with fluffy perihilar densities consistent with pulmonary edema. Ninety minutes after delivery, with an F_{IO_2} of 1.0, arterial blood gas analysis demonstrated a pH of 7.23, P_{CO_2} of 38 mm Hg, P_{O_2} of 177 mm Hg, bicarbonate of 16 mEq/L, and a base deficit of −11 mEq/L. Sodium bicarbonate (44 mEq) was administered, and the patient was transferred to the medical intensive care unit. An electrocardiogram demonstrated sinus tachycardia but no changes suggestive of ischemia. Continuous positive airway pressure of 12.5 cm H_2O by face mask provided some symptomatic relief, but the respiratory rate remained at 30–40 breaths/min. Arterial blood gas analysis during administration of 100% oxygen by continuous positive airway pressure mask showed a pH of 7.33, P_{CO_2} of 37 mm Hg, P_{O_2} of 393 mm Hg, bicarbonate of 19 mEq/L, and a base deficit of −6 mEq/L. Three hours after admission to the intensive care unit, the patient complained of fatigue and arterial oxygen saturation decreased to 89%. Tracheal intubation was deemed necessary. Cricoid pressure was applied, thiopental and succinylcholine were given, and intubation was performed. (The endotracheal tube was initially placed in the esophagus but was correctly repositioned in the trachea within 1 min. There was no evidence of aspiration.) Mechanical ventilation was instituted with positive end expiratory pressure of 5–8 cm H_2O. Peak inspiratory pressures were 40–46 cm H_2O.

Hypotension occurred after mechanical ventilation was initiated, but blood pressure improved with dopamine and dobutamine infusions. A pulmonary artery catheter demonstrated pulmonary artery pressure to be 45/31 mm Hg with a capillary wedge pressure of 18 mm Hg. Cardiac index by thermodilution was 1.9 $L \cdot min^{-1} \cdot m^{-2}$ with inotropic support. Calculated systemic and pulmonary vascular resistances were 2084 and 383 $dynes \cdot s \cdot cm^{-5}$, respectively. The coagulation profile was within normal limits except for fibrin degradation products, which were markedly elevated at >80 μg/mL, and a fibrinogen concentration, which was somewhat elevated at 429 mg/dL. The platelet count decreased from a baseline of 190,000/mm^3 to 78,000/mm^3 28 h after the onset of symptoms. There was no clinical evidence of excessive bleeding.

The patient's temperature reached a maximum of 38.4°C 14 h after the onset of dyspnea. All blood, urine, sputum, and placental cultures were negative. The pathologic examination showed the placenta to be normal without evidence of abruption or infarction. Analysis of pulmonary artery blood obtained approximately 10 h after the onset of dyspnea revealed no squamous cells or lanugo hairs. Direct immunofluorescence studies were difficult to interpret because of the presence of inflammatory cells.

With supportive care, the patient steadily improved and was extubated on the fourth postpartum day. An echocardiogram done on the sixth postpartum day revealed normal left ventricular function and the absence of valvular heart disease. Serial chest x-rays demonstrated clearing of the infiltrates by the ninth postpartum day. The patient was discharged home on the 11th postpartum day.

Discussion

We considered several possible etiologies for the acute onset of dyspnea and hypoxemia in this pregnant patient. Simple bronchospasm was unlikely because of the absence of wheezing and a clinical course consistent with adult respiratory distress syndrome. Fluid overload in a young healthy pregnant women should have caused a high cardiac output rather than a cardiac index of 1.9 $L \cdot min^{-1} \cdot m^{-2}$ with marked metabolic acidosis. There was no evidence of cardiac enlargement to suggest cardiomyopathy of pregnancy, nor was the clinical course consistent with this diagnosis. Thromboembolism can cause a marked elevation in pulmonary vascular resistance and a decrease in cardiac output. However, this patient demonstrated no clinical evidence of deep venous thrombosis, and she denied chest pain and produced no bloody sputum. Further, the chest x-ray showed bilateral pulmonary edema rather than the segmental regions of vascular lucency that would be expected in pulmonary embolic disease. Unfortunately, diagnostic tests such as ventilation perfusion scanning or pulmonary arteriography were not performed.

Aspiration pneumonitis may also cause an adult respiratory distress syndrome. This patient, however, had only one episode of vomiting, which occurred 5.5 h before her acute onset of dyspnea. Although pregnant women are at risk for aspiration, this patient was awake and alert and had received no sedation before vomiting. She received one 10-mg dose of nalbuphine 1 h before the onset of dyspnea, but she remained awake and alert. The patient received no other sedative drugs. The patient had no evidence of bronchospasm, and the radiologic findings were not consistent with the patchy or flocculent pulmonary infiltrates characteristic of aspiration.

The occurrence of dyspnea was temporally related to the institution of epidural anesthesia. If unintentionally injected intravascularly, the local anesthetic bupivacaine can be implicated in cardiovascular collapse. There is good evidence that this did not occur, primarily because the patient obtained the level of analgesia that would be expected from the epidural injection of drug. Further, there were no central nervous system symptoms or cardiac dysrhythmias suggestive of intravenous injection. Finally, the symptoms began 30 min after the epidural injection, whereas intravascular injection would have resulted in immediate symptoms because of high blood levels of drug.

Our patient demonstrated an acute onset of dyspnea, hypoxemia, and circulatory instability, which are signs of amniotic fluid embolism. The increased pulmonary vascular resistance and decreased cardiac output were also consistent with this diagnosis. Yet there are inconsistencies. Amniotic fluid embolism has a mortality rate as high as 86%, but our patient recovered completely from her critical illness. Pathologic evidence for fetal squamous cells, mucin, and lanugo hairs in pulmonary arterial blood were lacking. Coagulation abnormalities were present but were modest, and there was no clinical bleeding. Could these inconsistencies be explained by hypothesizing that our patient did not experience a spontaneous amniotic fluid embolism, but rather had an embolus of amniotic fluid diluted by the normal saline of the amnioinfusion? We wonder whether amnioinfusion at high infusion rates and pressures may predispose to entry of amniotic fluid into uterine vessels.

The onset of dyspnea was temporally related to the third 500-mL amnioinfusion. Normal saline was being infused via the intrauterine pressure catheter with an infusion pump (Abbott/Shaw Lifecare Pump, model IID, Abbott Laboratories, North Chicago, Ill.) at a rate of 999 mL/h (about 17 mL/min). It is possible that high pressures could have been generated during our technique of amnioinfusion. Pressures as high as 50 psi (2587 mm Hg) can be generated with this infusion pump before occlusion alarms sound and the pump stalls. Other reports of amnioinfusion (1,2) described infusing normal saline by gravity. One report (5) described an amnioinfusion rate higher than that used in this patient (1000 mL infused over 20–40 min) and one study (2) reported a comparable infusion rate (15–20 mL/min up to 800 mL total), but most (1,3,4,6) used slower infusion rates. No complications were reported in any of these studies.

In summary, we have reported a case of acute respiratory distress temporally associated with saline amnioinfusion in a healthy parturient. We consider amnioinfusion to be a useful procedure in situations of oligohydramnios and/or meconium staining of the amniotic fluid. We emphasize that a cause-and-effect relationship between amnioinfusion and respiratory failure was not established in this case. Rather, we report this case because of a temporal relationship between unexpected respiratory failure and a new procedure.

References

1. Miyazaki FS, Taylor NA. Saline amnioinfusion for relief of variable or prolonged decelerations. Am J Obstet Gynecol 1983;146:670–8.
2. Miyazaki FS, Nevarez F. Saline amnioinfusion for relief of repetitive variable decelerations: a prospective randomized study. Am J Obstet Gynecol 1985;153:301–6.
3. Nageotte MP, Freeman RK, Garite TJ, Dorchester W. Prophylactic intrapartum amnioinfusion in patients with preterm premature rupture of membranes. Am J Obstet Gynecol 1985;153:557–62.
4. Imanaka M, Ogita S, Sugawa T. Saline solution amnioinfusion for oligohydramnios after premature rupture of the membranes. Am J Obstet Gynecol 1989;161:102–6.
5. Wenstrom KD, Parsons MT. The prevention of meconium aspiration in labor using amnioinfusion. Obstet Gynecol 1989;73:647–51.
6. Sadovsky Y, Amon E, Bade M, Petrie R. Prophylactic amnioinfusion during labor complicated by meconium: a preliminary report. Am J Obstet Gynecol 1989;161:613–7.

Stellate Ganglion Blocks in Pediatric Patients

Winston C. V. Parris, MD, Bhaskar C. Reddy, MD, Houston W. White, MD, and David M. McGrath, MD

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—stellate ganglion block. SYMPATHETIC NERVOUS SYSTEM, GANGLIA—stellate. ANESTHESIA, PEDIATRIC—stellate block.

Stellate ganglion blocks (SGBs) (1) are used in adults for a variety of syndromes, including reflex sympathetic dystrophy, causalgia, herpes zoster, postherpetic neuralgia, Raynaud's syndrome, vasoconstriction of the vessels of the upper extremity, and a variety of chronic pain syndromes of the upper extremity. In pediatric patients, particularly patients under 6 yr of age, many of these diseases are not commonly seen, and, consequently, the indications for the performance of SGBs do not frequently arise in that patient population. We describe, because of this, two pediatric patients in whom we performed SGBs for two different clinical syndromes. As these conditions and other pain syndromes may become more frequently diagnosed, the need for the performance of SGBs in pediatric patients may increase.

Case 1

This patient was an 18-mo-old girl with a history of congenital vascular malformations affecting the thumb, index, and middle fingers of the left hand. These malformations had suddenly increased in size and had interfered with the development and functioning of the patient. Accordingly, the patient underwent percutaneous embolization of the digital venous malformations of the left hand. The postembolization course was complicated by vascular divergence to the second and third digits, interfering with circulation. The fourth digit developed severe ischemia of dermal layers with a capillary refill time >6 s in the third, fourth, and fifth digits. Before surgical exploration, the patient was referred to our Pain Control Center for possible nerve block therapy that might not only maximize perfusion before surgical exploration but also provide preoperative control of pain.

On examination, the patient was a 12-kg female with a major venous malformation of the left hand. There was no past history of any significant systemic illness other than the congenital vascular malformations of the left hand. The rest of her physical examination was essentially normal. Blood pressure was 120/59 mm Hg, pulse was 106 beats/min, and respiration was 28 breaths/min. Laboratory data included a hematocrit of 30.7%, platelet count 449,000/mm^3, prothrombin time 14 s, partial thromboplastin time 38 s, glucose 85 mg/dL, creatinine 0.6 mg/dL, and normal urinalysis. Medications included 5 mg meperidine administered intravenously every 3 h for pain and 12.5 mg acetaminophen with codeine elixir administered every 4 h.

The SGB was performed in the recovery room because we believed it would not be wise to perform a SGB in such a young patient without sedation. The patient was monitored using an electrocardiogram, Omega 1400 oscillometric blood pressure monitor, and pulse oximetry. After the insertion of an intravenous catheter, 0.15 mg atropine was administered intravenously and the patient was sedated with 1 mg/kg intravenous ketamine.

After the patient was adequately sedated, the neck was extended by placing a small towel between the scapulae. The entire neck and upper chest area were cleansed with Betadine solution and draped with sterile towels. The anterior tubercle of the sixth transverse process (Chassagniac's tubercle) was identified at the level of the cricoid cartilage and was immobilized between the second and third fingers with the same fingers retracting the carotid artery laterally along the anterior border of the sternoclei-

---

Received from the Department of Anesthesiology (Pain Control Center), Vanderbilt University Medical Center, Nashville, Tennessee. Accepted for publication December 1, 1990.

Address correspondence to Dr. Parris, Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN 37232.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

domastoid muscle. A 22-gauge regular needle, attached to a syringe containing 4 mL of 0.25% bupivacaine (10 mg), was inserted perpendicularly through the skin toward the anterior tubercle of the sixth transverse process. After bony contact was established, the needle was withdrawn approximately 1 mm while the hub of the needle was stabilized with the left hand resting on the anterior chest wall. The bupivacaine solution was injected after careful aspiration. Sequential aspirations were subsequently carried out after each milliliter of bupivacaine was injected. The patient remained immobile and moderately sedated throughout the entire procedure, and all aspirations through the needle were negative for blood or other fluids.

Shortly after the completion of the SGB, the ischemic hand became less cyanotic and the dark areas in the second, third, fourth, and fifth fingers looked healthier and pink. The color continued to improve except on the ventral aspect of the distal phalanx and intermediate phalanx of the fourth finger where some ischemia persisted. That the stellate ganglion was blocked was evidenced by a Horner's syndrome on the left side, conjunctival injection of the left eye, along with general hyperemia of the entire left upper extremity. Capillary refill time decreased to less than 3 s in the ischemic fingers approximately 1 h after the performance of the SGB. The patient was reevaluated 3 h after the block, and the general condition of the hand remained satisfactory. Capillary refill was maintained at less than 3 s. The patient appeared to be without pain and discomfort. Twenty-four hours and 48 h after the performance of the block, the circulatory status of the left hand remained good and the proposed surgery was canceled. The patient was seen in follow-up in the clinic 7 days later, and the circulatory state of the hand remained good. Pain also remained adequately controlled at that time.

Case 2

A 6-yr-old girl was admitted to our cardiology service with a history of sudden onset of syncope, brief periods of loss of consciousness, and an irregular heart beat. Before transfer to our institution from another hospital she was receiving a continuous lidocaine intravenous infusion preceded by a bolus intravenous injection of lidocaine, 2 mg/kg, for the above-mentioned symptoms. The patient's past medical history was unremarkable. The patient's mother died at 18 yr of age of an unknown cause. Further, the patient had an aunt who had a history of loss of consciousness and cardiac arrhythmias and who was also receiving medication for a seizure disorder. Because of the seriousness of the patient's arrhythmia and its hemodynamic consequences, she was transferred to the pediatric intensive care unit. The electrocardiogram showed sinus rhythm with intermittent premature ventricular contractions progressing to ventricular tachycardia. The Q-T interval was prolonged (0.55 s). The rhythm was consistent with "torsades des pointes" or familial prolonged Q-T syndrome. In spite of the lidocaine infusion, the patient developed breakthrough ventricular tachycardia, which progressed to cardiac arrest. The ventricular tachycardia was initially treated with intravenous isoproterenol and bretylium infusion. When cardiac arrest occurred, full advanced cardiac life support was instituted with the patient successfully resuscitated. She nevertheless continued to have frequent ventricular ectopy. A transvenous cardiac pacemaker was placed and was set at a rate of 120 beats/min with a good capture. Isoproterenol and bretylium infusions were discontinued, and medication with propranolol and phenytoin was initiated.

The patient continued to progress fairly satisfactorily until the sixth day after admission, when she developed severe ventricular ectopy leading to multifocal premature ventricular contractions that progressed to episodes of ventricular tachycardia. These intermittent episodes of ventricular tachycardia became continuous, producing loss of consciousness. At that point, the patient received cardiopulmonary resuscitation again for approximately 4 min and it was decided that the pacemaker had become ineffective. She underwent cardioversion with 20 W, which allowed the pacemaker to recapture at a rate of 150 beats/min. From a hemodynamic standpoint, she remained relatively stable afterward.

At that point, we were asked to perform a diagnostic left SGB for this patient to assess whether surgical stellate ganglionectomy might provide some sustained relief of her life-threatening cardiac symptoms. The following day we performed a left SGB with 5 mL of 0.25% bupivacaine. The customary signs of a successful SGB were not seen, but her general condition appeared to stabilize from a cardiac standpoint. She had no further ventricular ectopy and her pacemaker ran at a rate of approximately 130–140 beats/min. She remained asymptomatic and without any signs of ventricular ectopy for another 24 h. On the ninth day of admission she underwent placement of a permanent atrioventricular sequential pacemaker and also surgical left stellate ganglionectomy.

Postoperatively she developed a left Horner's syndrome. Approximately 6 h postoperatively she also developed ventricular ectopy that lasted for approximately 2 h. Her plasma phenytoin level was increased and she developed no further ventricular ectopy. On the 10th postoperative day her phenytoin and propranolol plasma levels were optimized and her general condition stabilized. She was evaluated with a 24-h Holter monitor, and no further evidence of ventricular ectopic activity was seen. She was discharged from the hospital on the 18th postoperative day after her parents were instructed and certified in cardiopulmonary resuscitation and basic life support. She was seen 1 wk later in the pediatric cardiology clinic and she continued to remain asymptomatic with no signs of ventricular ectopy.

Discussion

Chronic pain management is rapidly developing into a major subspecialty in modern medicine. Nerve block therapy is one of the modalities available to patients with chronic pain. Sympathetic blocks (2) in general and SGBs in particular have been widely used for the management of several acute and chronic pain syndromes, including reflex sympathetic dystrophy (3), causalgia, sympathetically mediated pain, herpes zoster (4), postherpetic neuralgia, Raynaud's syndrome, Raynaud's phenomenon, unilateral headache (5), and vascular insufficiency syndromes. Stellate ganglion blocks have also been used to treat chest pain secondary to angina pectoris (6) and primary pulmonary hypertension (7). However, most of these syndromes have been almost exclusively diagnosed in adults.

One of the goals of health-care providers for the 1990s has been to bring the management of chronic pain in pediatric patients to the forefront of chronic pain management. There has been a misconception that very young pediatric patients do not experience pain (8). This misconception was compounded by the fact that there were very few reliable and reproducible methods for measuring pain, not only in adults but also in pediatric patients. With renewed interest in chronic pain in pediatric patients, it is very likely that more chronic pain syndromes in the pediatric patient population will be investigated and diagnosed, and appropriate treatment strategies developed. Thus, it may be helpful to describe and to report on the use of one of the more frequently used nerve blocks in the management of pain and other medical problems in pediatric patients, stellate ganglion block.

In the first case report, the patient had major vascular insufficiency, secondary to congenital venous malformations, which produced ischemic changes. The resulting sympathetic blockade of the upper extremity induced by the SGB produced vasodilation not only of the large and middle order vessels, but also significant vasodilation at the capillary level. This sympathetic blockade and subsequent vasodilation was dramatic not only in that the effect was almost instantaneous, but also in that it was sustained for a long period. The efficacy of this block negated the need for major vascular surgery in a very small infant in whom the morbidity would not have been insignificant. It is very likely that congenital vascular malformations may occur with sufficient frequency to make this procedure applicable in cases in which ischemia and impending infarction are present. To the best of our knowledge, the frequency of Raynaud's phenomenon or syndrome has not been reported in children (9), and these conditions may be either undertreated or undiagnosed. With the availability and demonstrated efficacy of SGB in treating these vascular phenomena, it is likely that health-care providers may be more prone to use these methods in the management of pediatric patients with peripheral vascular insufficiency.

With regard to the second case report, many reports have been published indicating that patients with prolonged Q-T syndromes and cardiac arrhythmias respond favorably to SGB (10). The association of a prolonged Q-T syndrome, congenital deafness, mutism, and syncopal attacks secondary to ventricular dysfunction after emotional or physical stress (the Jervell–Lange-Nielsen syndrome [11]), is associated with sudden death in children. When the congenital deafness is absent in this syndrome (but the other cardiovascular signs and symptoms are present) the condition is referred to as the Romano–Ward syndrome (12,13). Both of these conditions have high mortality rates and are a major cause of sudden death in children. The pathogenesis of these syndromes is not well understood, and treatment is currently based on symptoms and is supportive.

Several reports (14,15) have indicated that left SGBs can be life-saving by interrupting acute episodes of ventricular tachyarrhythmias in patients with the above syndromes. The more definitive treatment is a surgical stellate ganglionectomy or surgical cervical sympathectomy. These syndromes, although not common, occur with sufficient frequency to make it important for anesthesiologists to be aware of their existence and the role of SGBs in their management. There are no reliable data on the frequency of these syndromes, but in our institution we have had three patients in 5 yr who required SGB therapy for tachyarrhythmias secondary to prolonged Q-T syndrome. There has been some controversy as to whether a left or right SGB would be more effective. Prolongation of the Q-T interval with a right SGB has been reported, as has shortening of the Q-T interval with a left SGB (16), although unpublished observations by other workers showed no change in the Q-T interval after either left or right SGB. Indeed, although prolongation of the Q-T interval has been reported after both left and right SGB (17), further studies have demonstrated significant prolongation of the functional refractory period exclusively in the lateral and posterior left ventricle of the cat after left SGB (18). That there are other cardiac effects of SGBs (in addition to the effects on the dromotropic activity of the heart) is suggested by the observation that left SGBs affect mainly the inotropic effect of the myocardium whereas right SGBs affect mainly chronotropic activity of the myocardium (19). It is very likely that all the above studies may well have some relevance to the clinical picture, but this is definitely not yet clearly elucidated. Therefore, it becomes necessary for anesthesiologists to be familiar with these syndromes and the possible therapeutic role of SGBs in the management of these patients.

The younger and therefore the smaller the patient, the more difficult it is to obtain cooperation of the patient for the performance of SGBs. In a crying or active infant who is unlikely to remain still, serious damage to structures contiguous to the stellate ganglion (e.g., vertebral artery, carotid artery, trachea, anterior jugular vein, thyroid gland, and brachial plexus) may occur during a performance of this block. To facilitate the safe performance of this block, sedation may become necessary. We chose intravenous ketamine in case 1 because it has antiarrhythmic properties and does not depress the respiration as readily as thiopental and most of the other sedatives and tranquilizers. (Case 2 did not require sedation because the patient was already sedated from a prior procedure.) The tachycardia after ketamine administration may be beneficial in the event of any vagal response from inadvertent pressure on the carotid body during the performance of the SGB. Ketamine, on the other hand, may cause an accumulation of oropharyngeal secretions that may produce laryngospasm and subsequent respiratory difficulties. In anticipation of these undesirable potential complications, the patient was given intravenous atropine before the administration of ketamine. Because this procedure and subsequent sedation is associated with some degree of morbidity, basic monitoring and intravenous access must be obtained beforehand. The monitoring used in both patients consisted of electrocardiogram, oscillometric blood pressure monitoring, pulse oximetry, and careful patient observation. It is also necessary to have available the routine anesthetic drugs including thiopental (to abort any seizure activity that may develop) and succinylcholine (to facilitate tracheal intubation if necessary), as well as other resuscitative drugs. An anesthesia machine—or, in its absence, a self-inflating bag with face masks, airway, laryngoscope, suction device, endotracheal tubes, and oxygen source—is necessary to deal with any ventilatory dysfunction that may occur.

In conclusion, we describe two clinical syndromes in pediatric patients that were treated with SGBs. The syndromes included vascular insufficiency secondary to congenital vascular malformation and the Romano–Ward syndrome consisting of prolongation of the Q-T interval with life-threatening cardiac dysarrhythmias. Both patients responded satisfactorily to SGBs, and we recommend that this technique be available in the anesthesiologist's armamentarium for treating these and related syndromes.

References

1. Carron H, Litwiller R. Stellate ganglion block. Anesth Analg 1975;54:567–71.
2. Bonica JJ. The management of pain. 2nd ed. Philadelphia: Lea & Febiger, 1990.
3. Bonelli S, Conoscente F, Movilia PG, et al. Regional intravenous guanethidine vs. stellate ganglion block in reflex sympathetic dystrophies: a randomized trial. Pain 1983;16:267–70.
4. Colding A. Treatment of pain. Organization of a pain clinic: treatment of acute herpes zoster. Proc R Soc Med 1973;66: 541–7.
5. Parris WCV, Jamison RN, Lin S, Kambam JR. The use of stellate ganglion blocks in treating unilateral migraine headaches. Reg Anesth 1988;13(Suppl 1):78.
6. Feigl EO. Sympathetic control of the coronary circulation. Circ Res 1967;20:262–5.
7. Parris WCV, Lin S, Frist W. Use of stellate ganglion blocks for chronic chest pain associated with primary pulmonary hypertension. Anesth Analg 1988;67:993–5.
8. Apley J. Pain and childhood. J Psychosom Res 1976;20:383–9.
9. Spittell JA, Jr. Raynaud's phenomenon and allied vasospastic disorders. In: Jurgens JL, Spittell JA Jr, Fairbairn JF, eds. Peripheral vascular diseases, 5th ed. Philadelphia: WB Saunders, 1980:555–83.
10. Yanagida H, Kemi C, Suwa K. The effects of stellate ganglion block on idiopathic prolongation of the Q-T interval with cardiac arrhythmia (the Romano–Ward syndrome). Anesth Analg 1976;55:782–7.
11. Jervell A, Lange-Nielsen F. Congenital deaf-mutism: functional heart disease with prolongation of Q-T interval and sudden death. Am Heart J 1957;54:59–68.
12. Ward OC. A new familiar cardiac syndrome in children. J Ir Med Assoc 1964;54:103–6.
13. Romano C, Genrme G, Pongiglion R. Aritmie cardiache rare delleta pediatrica. Clin Paediatr 1963;45:656–61.
14. Lloyd R, Okada R, Stagg J, et al. The treatment of recurrent ventricular tachycardia with bilateral cervicothoracic sympa-

thetic ganglionectomy. A report of 2 cases. Circulation 1974; 50:382–4.

15. Milne JR, Ward DE, Spurrell AJ, Camm AJ. The long Q-T syndrome: effects of drugs and left stellate ganglion blocks. Am Heart J 1982;104:194–8.
16. Moss AJ, McDonald J. Unilateral cervico-thoracic sympathetic ganglionectomy for the treatment of long Q-T interval syndrome. N Engl J Med 1971;285:903–4.
17. Vincent GM, Abildskov JA, Burgess MJ. Q-T interval syndromes. Prog Cardiovasc Dis 1974;16:523–30.
18. Rogers MC, Abildskov JA, Preston JB. Cardiac effects of stimulation and block of stellate ganglion. Anesthesiology 1973;39:525–33.
19. Randall WC, Rohse WG. The augmentor action of the sympathetic cardiac nerves. Circ Res 1956;4:470–5.

ANESTH ANALG 1991;72:557–8

Acute Dystonia After Alfentanil in Untreated Parkinson's Disease

Berend Mets, MB, ChB, FFARCS(Eng), FFA(SA)

Key Words: ANALGESICS, ALFENTANIL. COMPLICATIONS, PARKINSON'S DISEASE.

There is evidence from animal experiments that opioids may induce parkinsonism through decreased central dopaminergic transmission (1), but there has been little discussion of this possibility in humans (2).

We present a patient with untreated Parkinson's disease who developed an acute dystonic reaction after the administration of alfentanil.

Case Report

A 79-yr-old woman with bilateral acute angle glaucoma was scheduled for a trabeculectomy of her right eye. Seven months earlier she had been diagnosed as having Parkinson's disease after admission to hospital for a left-sided cerebral vascular accident (CVA). A computed tomography scan of the head performed at that time revealed no local pathology. Although she had received treatment for hypertension and glaucoma in the past, she was taking no medications at the time of her present admission except for diclofenac for osteoarthritis.

At the preoperative visit, the patient was found to have the following features of Parkinson's disease: masklike facies, slow slurred speech, lead pipe rigidity in both arms, a pill-rolling tremor (especially of the right hand), difficulty in initiating movement, poor balance, and a shuffling gait with poverty of motion. There was no evidence of residual weakness from the previous CVA. She was normotensive (150/90 mm Hg), afebrile, and weighed 57.5 kg.

Except for an electrocardiogram, which revealed ischemic changes of indeterminate age, there was no further evidence of systemic disease. She had never been anesthetized. Premedication was 5 mg oral diazepam 2 h before the procedure.

Induction of anesthesia after 3 min of preoxygenation was monitored with an electrocardiogram, an automated sphygmomanometer, and pulse oximetry. The patient's heart rate immediately before induction was 72 beats/min, her blood pressure was 191/106 mm Hg, and her oxygen saturation was 97%. Glycopyrrolate, 0.2 mg, was administered via an in-dwelling cannula. A minute later blood pressure was 210/116 mm Hg, and heart rate was unchanged. One milligram of alfentanil was then administered over 10 s while preoxygenation was continued. Approximately 1 min after this, the pill-rolling tremor of the hands markedly increased and the patient raised both arms, apparently involuntarily. This progressed to total body rigidity with opisthotonus and an oculogyric crisis with a fixed gaze to her right.

Communication with the patient was lost and the intern at the patient's head could not prise open her mouth due to muscle spasm. The oxygen saturation was 96%. There was no clonic activity or incontinence simulating a seizure. Intravenous induction of anesthesia was completed with 14 mg etomidate, and 28 mg atracurium was administered to facilitate tracheal intubation. Ventilation of the patient's lungs by hand using an anesthesia face mask was found to be difficult until the onset of paralysis, but the oxygen saturation did not decrease below 95% at any time. Her trachea was intubated and anesthesia was maintained with nitrous oxide in oxygen (FIO_2, 35) and 0.8% enflurane. Atracurium was administered for muscle relaxation as necessary. During the course of the 45-min operation, the patient developed ventricular extrasystoles and required intervention for both hypertension (isoflurane) and hypotension (5 mg ephedrine). She recovered without neurologic deficit. On questioning postoperatively, she denied any history of seizures or dystonia.

Discussion

Movement disorders are an occasional feature of induction of anesthesia with alfentanil. This may

---

Received from the Departments of Clinical Pharmacology and Anesthesia, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa. Accepted for publication December 3, 1990.

Address correspondence to Dr. Mets, Departments of Clinical Pharmacology and Anesthesia, University of Cape Town and Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

present as muscle rigidity (3) or as a seizure (4). Although similar in many respects to alfentanil-induced rigidity, the reaction in this patient differed in that the first manifestation was that of worsening of her pill-rolling tremor, followed by arm and body rigidity with opisthotonus and an oculogyric crisis. In contrast, in a study of 10 patients, Benthuysen et al. (3) found that on infusing 175 μg/kg of alfentanil over 1 min, the typical rigidity that was induced resulted in atlantooccipital flexion without associated tremor or oculogyria. Furthermore, classical opioid-induced rigidity is usually dose-related and is only marked at higher doses (4). The reaction in our patient also differed from the first report of a seizure associated with alfentanil (4). In the latter, the patient developed coarse jerking rhythmical movements in the absence of rigidity. Thus the reaction in our patient was more in keeping with an acute exacerbation of parkinsonism.

Parkinson's disease is due to a selective dopamine deficiency in the putamen and caudate nucleus of the basal ganglia (5). Therapy usually includes levodopa and anticholinergic drugs. These were contraindicated in this patient as they have the potential for worsening acute angle glaucoma. It is conceivable that the absence of this therapy could have made her more susceptible to extrapyramidal reactions from antidopaminergic drugs.

Investigations in animals suggest that opioids interact with the dopaminergic nigrostriatal system. Puri et al. (1) have, for example, shown in rats that the acute effect of morphine both neurochemically and behaviorally resembles the dopaminergic blocking action of haloperidol. Morphine has also been shown to inhibit the release of striatal dopamine in vitro (6).

Wand et al. (7) suggest that this morphine-induced inhibition of dopaminergic transmission is presynaptic in nature; Hirschhorn et al. (8) implicate a postsynaptic action. It is interesting that the opioid-induced rigidity and catalepsy in the rat model of Wand et al. (7) was reversed by the administration of levodopa.

This is the first report of the acute exacerbation of parkinsonism associated with the use of alfentanil. Because morphine has antidopaminergic actions, and because alfentanil (like morphine) is a μ-receptor agonist (9), it is conceivable that alfentanil could have precipitated this reaction through an inhibition of dopaminergic transmission in the basal ganglia.

That alfentanil precipitated this reaction is supported by the very close temporal relationship to its administration. It is unlikely that glycopyrrolate can be implicated because this drug does not cross the blood-brain barrier (10) and would improve rather than worsen the parkinsonism.

The patient was also given diazepam as premedication as well as the nonsteroidal analgesic diclofenac. Diazepam, if anything, would have alleviated the reaction. There are sporadic reports of extrapyramidal side effects with nonsteroidal antiinflammatory drugs (11,12). It is unlikely that diclofenac, administered the previous evening, could be implicated directly. However, there is a potential for a transiently higher free fraction of alfentanil in the presence of both diclofenac and diazepam due to their strong plasma protein binding.

In summary, we have described a patient with untreated Parkinson's disease who developed an acute dystonic reaction after alfentanil administration. Animal experiments indicate that this reaction may be due to opioid-induced decreased central dopaminergic transmission. This case report suggests caution in the administration of opioids to such patients and the need for optimal control of parkinsonism preoperatively.

The author thanks both Dr. A. H. Robins and Professor M. F. M. James for their helpful comments.

References

1. Puri SK, Reddy C, Lal H. Blockade of central dopaminergic receptors by morphine: effect of haloperidol, apomorphine or benztropine. Res Commun Chem Pathol Pharmacol 1973;5:389–401.
2. Severn AM. Parkinsonism and the anaesthetist. Br J Anaesth 1988;61:761–70.
3. Benthuysen JL, Ty Smith N, Sanford TJ, Head N, Dec-Silver RN. Physiology of alfentanil-induced rigidity. Anesthesiology 1986;64:440–6.
4. Strong WE, Matson M. Probable seizure after alfentanyl. Anesth Analg 1989;68:692–3.
5. Marsden CD. Parkinson's disease. Lancet 1990;i:948–52.
6. Loh HH, Brase DA, Sampath-Khan S, Mar JB, Leong Way E. β-endorphin in vitro inhibition of striatal dopamine release. Nature 1976;264:567–8.
7. Wand P, Kuschinsky K, Sontag KH. Morphine-induced muscular rigidity in rats. Eur J Pharmacol 1973;24:189–93.
8. Hirschhorn ID, Hittner D, Gardner EL, Cubells J, Makman MJ. Evidence for a role of endogenous opioids in the nigrostriatal system: influence of naloxone and morphine on nigrostriatal dopaminergic supersensitivity. Brain Res 1983;270:109–17.
9. Cookson RG, Niemegeers CJE, Bussche G. The development of alfentanyl. Br J Anaesth 1983;55:147S–55S.
10. Ali-Melkhila TM, Kaila T, Konto J, Lisalo E. Pharmacokinetics of im glycopyrronium. Br J Anaesth 1990;64:667–70.
11. Enevoldsen TP, Wiles CM, Sawle GV. Acute parkinsonism associated with fluribrofen. Br Med J 1990;300:540–1.
12. Sandyk R, Gillman MA. Acute exacerbation of parkinson's disease with sulindac. Ann Neurol 1985;17:104–5.

Venous Air Embolism Occurring After Removal of a Central Venous Catheter

W. Sherman Turnage, MD, and James V. Harper, MD

Key Words: EMBOLISM, AIR.

Venous air embolism is a well-known risk of central venous catheter placement in critically ill patients. However, clinicians may not be aware that venous air embolism can also occur after removal of a central venous line. Described in the following two case reports are what are believed to be episodes of air embolism after removal of central lines.

Case 1

A 77-yr-old woman was admitted to St. Luke's Hospital for repair of an abdominal aortic aneurysm. A balloon-tipped, flow-directed pulmonary artery catheter was inserted using a Cordis sheath in the right internal jugular vein after the induction of general anesthesia. She then underwent uneventful repair of the aneurysm and was transferred out of the surgical intensive care unit on the second postoperative day after an uneventful course in the unit. At the time of transfer the pulmonary artery catheter was removed, but the Cordis sheath was left in place. On the fourth postoperative day the Cordis sheath was removed and a dressing of povidone-iodine ointment and 2 × 2 gauze was placed over the wound with a single strip of adhesive tape. Approximately 15 min after the Cordis sheath was removed, she walked to the bathroom, and within moments of standing she complained of feeling dizzy. When she returned from the bathroom the nurse helping her reported that she suddenly collapsed onto the bed and became unresponsive to verbal queries, although she had her eyes open. On telemetry monitoring she was found to have a sudden increase in heart rate from 85 to 120–130 beats/min, and her blood pressure increased from 120/80 to 190/95 mm Hg. After 2 min the episode resolved. Arterial blood gas tensions while breathing with 4 L/min oxygen flowing through a nasal cannula showed a decrease in $\mathrm{Pa}_{\mathrm{O}_2}$ from 80 mm Hg that morning to 42 mm Hg immediately after the episode. A chest radiograph was unchanged from the morning film, revealing only a small area of atelectasis in the left base. A pulmonary ventilation/perfusion scan and pulmonary angiogram were done; they revealed no evidence of pulmonary embolus. The hypoxemia resolved with 50% oxygen by mask, and she was monitored in the intensive care unit overnight. The patient made an uneventful recovery and was discharged home several days later.

Case 2

A 67-yr-old man was admitted to St. Luke's Hospital for chemotherapy for metastatic squamous cell carcinoma of the larynx. Because the intervals between chemotherapy courses were 2–3 mo, a central venous catheter was placed each time he came in for treatment. On this admission a triple-lumen central venous line was placed in the left internal jugular vein. He completed a 10-day course of chemotherapy without incident, and on the day before discharge the catheter was removed. A dressing of gauze and adhesive tape was placed over the wound after the nurse exerted pressure on the area for 10 min. Immediately after the dressing was applied, the patient sat up in a chair, and within 2 min he complained of feeling dizzy. He was promptly placed back into bed. However, by that time he had suffered a cardiac arrest from which he could not be resuscitated. Permission for an autopsy was not granted.

Discussion

The relationship of both episodes related above to the prior removal of a central venous catheter suggests

---

Received from the Department of Anesthesiology, Mayo Clinic, Jacksonville, Florida; and the Department of Anesthesiology, Mayo Graduate School of Medicine, Rochester, Minnesota. Accepted for publication December 5, 1990.

Address correspondence to Dr. Harper, Department of Anesthesiology, Mayo Clinic, Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224.

©1991 by the International Anesthesia Research Society
0003-2999/91/$3.50

that the direct cause of each event was the entrainment of air through the tract formed by the device. In the first patient, pressure had been applied to the site for 10 min, and there was no bleeding noted when the dressing was applied; but when the patient became unresponsive blood was seen oozing from the site. Myocardial ischemia and infarction were excluded by serial electrocardiograms and by normal serum levels of cardiac enzymes; a neurologic consultant also found no evidence for cerebral vascular insufficiency. Because her symptoms and hypoxemia were compatible with pulmonary thromboembolism, this etiology was pursued, but no evidence for an embolus could be found within 3–4 h of the event. The most likely explanation for the event in light of the fact that other possible etiologies were excluded is air embolism that dissipated by the time the pulmonary angiogram was done. The second patient had no history of cardiac disease and was clearly not in a terminal state, but because he was not being monitored at the time the catheter was removed other causes of sudden cardiac arrest cannot be ruled out. Nevertheless, it is noteworthy that both patients had assumed an upright position after removal of a central venous catheter, and both patients were slightly dehydrated on clinical examination before these reported incidents.

Air embolism occurs when the pressure in a vein open to air decreases below atmospheric pressure. These conditions are met during craniotomy in the sitting position, when the level of the venous channels in the skull and dural sinuses are above the level of the heart. This situation also occurs during insertion of vascular catheters in the large veins of the neck. During the insertion of a noncollapsible catheter open to air, deep inspiration by the patient causes the intrathoracic pressure to decrease below ambient pressure, thus entraining air through the catheter (1). It is possible that this mechanism was responsible for air embolism in these patients because each had a catheter in place long enough for a fibrinous tract to form that could remain open after the removal of the device. Additionally, maneuvers such as coughing or straining that would increase the venous pressure immediately after the removal of a catheter might dislodge freshly formed clot, allowing the tract to reopen on the vascular side. The lack of a dressing impermeable to air would allow air to be entrained through a tract during inspiration, when the venous pressure would fall, particularly in dehydrated patients, if clot from the site had been dislodged.

Indeed, this complication of central venous catheter removal has been reported twice before (2,3). The patients in both reports had episodes similar to those reported here. In both cases the authors point out that the catheters were removed when the patients were in an upright position, and neither patient had an occlusive dressing applied. One patient suffered a cardiac arrest and was left in a permanent vegetative state (3); the other patient developed pulmonary edema secondary to pulmonary air embolism and subsequently recovered (2).

Because the outcome of inadvertent venous air embolism associated with the removal of a central venous catheter can be disastrous, if not fatal, we wish to alert anesthesiologists and other physicians who use these devices to this potential complication. Although measures to prevent air embolism are commonly taken during *insertion* of a catheter by use of Trendelenburg's position and having the patient breath-hold during passage of the guidewire, we wish to stress that similar measures should accompany the *removal* of the catheter. Because of the two cases described here, we have instructed the nurses at our hospital to remove central lines with the patient in the supine position, place an occlusive dressing over the site, and then keep the patient at bed rest for 1 h. With proper attention to detail, venous air embolism should be an entirely avoidable complication of central line placement and removal.

References

1. O'Quin R, Lakshminarayan S. Venous air embolism. Arch Int Med 1982;142:2173–6.
2. Kuhn M, Fitting J, Leuenberger P. Acute pulmonary edema caused by venous air embolism after removal of subclavian catheter. Chest 1987;92:364–5.
3. Mendieta J, Roy T, Denny D, Ossorio M. Venous air embolism associated with removal of central venous catheters. J Ky Med Assoc 1988;86:169–73.

ANESTH ANALG 1991;72:561–7

Letters to the Editor

Is Observing the Patient a Thing of the Past?

Key Words: MONITORING, PATIENT OBSERVATION.

To the Editor:

I believe an oversight in the letter by Sosis and Sisamis (1) highlights one of the major concerns those of us who have practiced anesthesia and trained residents over a period of many years have. That is, we now have a specialty that has lost sight of the fact that monitors are merely extensions of our senses. Nowhere in the letter is any mention made of watching the chest move and using the precordial stethoscope to listen for breath sounds. No one would argue against the fact that in the patient with a large barrel chest, massive obesity, etc., it may be extremely difficult to determine whether an endotracheal tube is in the trachea or esophagus. On the other hand, I contend that in the vast majority of patients (and probably in Dr. Sosis' patient as well) a quick look at the chest would have revealed the correct placement of the tube earlier than the desaturation recorded by the pulse oximeter. I have personally watched a resident extubate an intubated patient on the basis of no carbon dioxide wave form on a capnograph. The patient's chest was moving well, but the capnograph had not been placed within the breathing circuit.

I would like to emphasize that I am in absolute agreement with those that suggest that capnography and pulse oximetry are invaluable aids to the conduct of anesthesia and give insights into, and early warnings of, many of the critical incidents that occur during anesthesia. I also, however, believe that they have been a two-edged sword because they have increased dramatically the tendency to rely on monitors rather than observe patients closely, and have led to delays in diagnosis and treatment of some problems while the determination is made whether it is a patient problem or monitor failure. One need only read Arthur Keats' superb article (2) to get a further feel for the problem I am addressing.

I am not suggesting that Dr. Sosis did not look for movement of the chest. I am only pointing out that his letter, which discusses confirmation of correct placement of an endotracheal tube, does not even mention this or any other clinical sign used to detect correct endotracheal tube placement.

The whole issue of where monitors fit into the diagnostic process requires careful reevaluation by the specialty. Is observing the patient a thing of the past? I hope not.

Gerald Edelist, MD, FRCP(C)
Department of Anaesthesia
University of Toronto
Room 132, Fitzgerald Building
150 College Street
Toronto, Ontario M5S 1 A8
Canada

References

1. Sosis MB, Sisamis J. Pulse oximeter in confirmation of correct tracheal tube placement (letter to the editor). Anesth Analg 1990;71:309–10.
2. Keats AS. Anesthesia mortality in perspective. Anesth Analg 1990;71: 113–9.

In Response:

I wish to thank Dr. Edelist for his interest in our report "Pulse Oximetry in Confirmation of Correct Tracheal Tube Placement" (1). Our aim in presenting this information was to point out that although capnography has been touted as the best way to distinguish between tracheal and esophageal placement of an endotracheal tube, it too may fail. This is important because undetected esophageal intubation is life-threatening. We believe that careful auscultation, observation, and use of instrumentation (i.e., capnography and pulse oximetry) are all necessary to verify that endotracheal tube placement is correct.

The observation of the anesthetized patient using the anesthesiologist's own sensory modalities and the information provided by modern instrumentation is the foundation of our specialty and cannot be stressed too much. We would certainly be remiss if we suggested otherwise.

Mitchel B. Sosis, MD, PhD
Department of Anesthesiology
Rush Presbyterian–St. Luke's Medical Center
Chicago, IL 60612

Reference

1. Sosis MB, Sisamis J. Pulse oximetry in confirmation of correct tracheal tube placement. Anesth Analg 1990;71:309–10.

©1991 by the International Anesthesia Research Society

A Case for the Removal of the Retained Intrathecal Catheter

Key Words: ANESTHETIC TECHNIQUES, SPINAL—continuous. COMPLICATIONS, RETAINED CATHETER.

To the Editor:

We were recently faced with a retained spinal catheter that we found needed to be surgically removed.

The patient was a 21-yr-old woman who had undergone an anterior-posterior spinal fusion. A 27-gauge spinal catheter was placed intraoperatively and was tunneled subcutaneously so as to exit through the skin 4 cm from the midline. Intrathecal morphine was injected through the catheter after free aspiration of cerebrospinal fluid. Excellent postoperative analgesia was achieved by intermittent intrathecal injections of morphine. After the final injection, the catheter could not be removed by gentle traction. Fluoroscopy, after the injection of a small amount of metrizomide through the catheter, showed it clearly to be in the intrathecal space, but taking a tortuous course around the spinal rods. A more forceful attempt to withdraw the catheter caused it to snap off at the skin, and approximately 6 cm of the catheter retracted below surface level. The patient was initially managed expectantly. There remained concern, however, that the catheter could act as a wick to drain cerebrospinal fluid. Additionally, because of the proximity of the catheter to the surgical hematoma, a wound infection might extend intrathecally. On the fourth postoperative day, the patient underwent a small exploration of the most distal area of the wound. The catheter was found to be wrapped 270° around one of the spinal rods and was easily removed. The remainder of the hospital course was uncomplicated. The patient had no infectious or neurologic sequelae either from the presence of the catheter in the subarachnoid space for 2 days or from its removal.

There is a paucity of reports of retained intrathecal catheters (1). As the use of intrathecal catheters increases (and the diameter decreases) (2), the risk of this potential complication increases. Whether a retained intrathecal catheter always needs to be removed is debatable (3), if, however, the retained catheter is near the surgical incision, its removal may be warranted to avoid a potential neurologic intrathecal spread of infection via the catheter tract in the event of a wound infection.

Carol A. Pasquariello, MD
Department of Anesthesia and Critical Care
St. Christopher's Hospital for Children
Front Street at Erie
Philadelphia, PA 19134

Randal R. Betz, MD
Department of Orthopedic Surgery
Temple University School of Medicine
Philadelphia, PA 19133

References

1. Baxter AD. Microcatheters for continuous spinal anesthesia. Anesth Analg 1990;71:200–1.
2. Hurley RJ, Lambert DH. Continuous spinal anesthesia with a microcatheter technique: preliminary experience. Anesth Analg 1990;70:97–102.
3. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.

Blood Pressure Values in Parturients: Auscultatory Versus Oscillatory Values

Key Words: ANESTHESIA, OBSTETRICAL—blood pressure. BLOOD PRESSURE, OBSTETRICAL.

To the Editor:

Blood pressure (BP) values obtained by the Riva-Rocci auscultatory method are not identical with those observed with the oscillatory method. Weaver et al. (1), in 381 children aged 10–13 yr, found that oscillatory systolic pressures were 5–8 mm Hg higher than the auscultatory values, whereas diastolic pressures were 8–9 mm Hg lower. The significance of these differences in parturients has not been ascertained. With permission of our Committee on Clinical Investigations, a study was initiated comparing, in term parturients in labor, the results of the auscultatory method with those that measure BP based on an oscillatory method. (The need for written informed patient consent was waived by the Committee on Clinical Investigations.) We used a Dinamap monitor model 1846 SX (Criticon Inc., Tampa, Fla.), the calibration of which had been tested by our Bioengineering Department and found to be accurate according to the manufacturer's specifications (2). Minor rearrangement of the tubing of the Dinamap device permitted use of the same cuff for auscultatory measurement of BP too. An interval of at least 2 min separated the measurements, with the auscultatory method preceding the oscillatory. The measurements, always made in the absence of uterine contractions, were repeated twice within 20 min.

The findings in the first 12 parturients studied (four in early labor, eight in advanced labor) are sufficiently pertinent to warrant a preliminary report. In all 12 women, systolic pressures were always higher and diastolic pressures were always lower with the Dinamap monitor than they were with the auscultatory method both before and after institution of lumbar extradural analgesia. The differences ranged from 5 to 18 mm Hg (mean, 10.2 ± 3.7 mm Hg) in systolic pressure and from 4 to 14 mm Hg (mean, 9.9 ± 3.0 mm Hg) in diastolic pressure. The differences in auscultatory pressures between two observers (D.R.S. and S.I.W.) were 0–2 mm Hg. A representative case was that of a healthy 21-yr-old primigravida in early labor who developed vena cava compression syndrome when lying supine in bed. With the auscultatory method, her BP was 90/68 mm Hg with a calculated mean pressure of 75 mm Hg;

with the Dinamap monitor, the BP was 108/62 mm Hg with a mean of 80 mm Hg.

In normotensive parturients, based on auscultatory measurements, hypotension has been defined as a systolic pressure below 100 mm Hg (3,4). According to our findings, this definition must be revised when an automated BP device is employed.

Gertie F. Marx, MD
David R. Sofair, MD
Scott I. Winikoff, MD
Department of Anesthesiology
Albert Einstein College of Medicine
1300 Morris Park Avenue
Bronx, NY 10461

References

1. Weaver MG, Park MK, Lee D-H. Differences in blood pressure levels obtained by auscultatory and oscillometric methods. Am J Dis Child 1990;144:911–4.
2. DINAMAP™ Adult/Pediatric and Neonatal Vital Signs Monitor Model 1846—Operation Manual. Tampa, Fla.: Critikon, Inc., 1984.
3. De la Vega SB. Effects of vertebral blocks on the cardiovascular system. In: Aboulesh E, ed. Pain control in obstetrics. Philadelphia: JB Lippincott Company, 1977:103.
4. Shnider SM, Levinson G. Anesthesia for cesarean section. In: Shnider SM, Levinson G, eds. Anesthesia for obstetrics. 2nd ed. Baltimore: Williams & Wilkins, 1984:162.

A Simple Device to Monitor Neuromuscular Blockade

Key Words: MONITORING, NEUROMUSCULAR FUNCTION. NEUROMUSCULAR TRANSMISSION, MONITORING.

To the Editor:

Widespread use of neuromuscular blocking agents during general anesthesia has made monitoring of the degree of muscle blockade an inherent part of a safe anesthetic management (1–3). Surface stimulation of the ulnar nerve allows the measurement of the adduction of the thumb by a force displacement transducer or an accelograph. Unfortunately, impracticality and high cost may preclude their routine use under clinical conditions.

We have designed a simple apparatus to monitor neuromuscular blockade—one that is easy to set up from common devices found in the operating room and that displays the force of contraction of the adductor pollicis muscle on a monitor screen, thereby providing an objective method for measurement of the T4/T1 ratio.

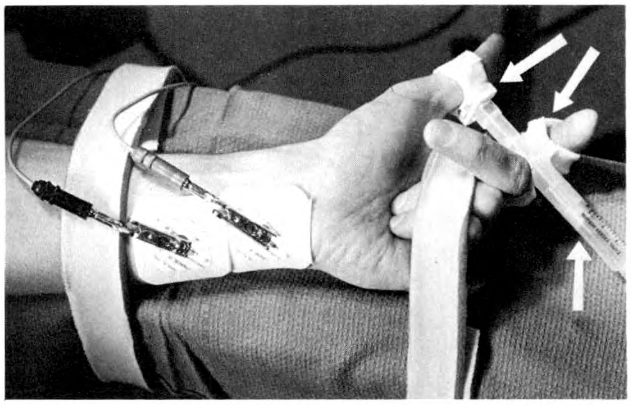


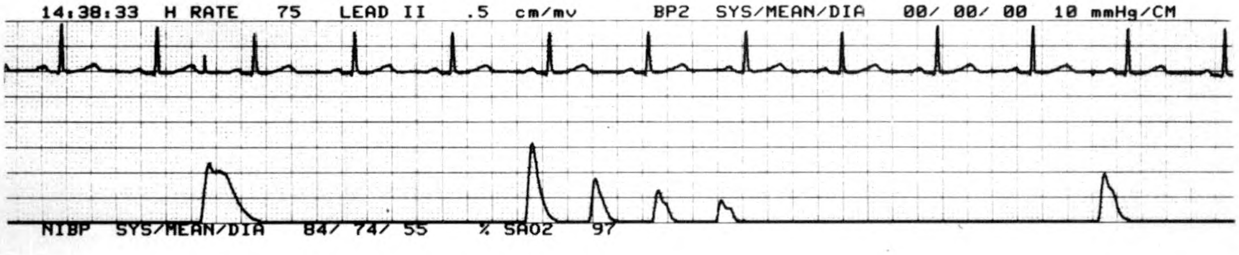
Figure 1. A plastic blood gas syringe filled with 3 mL of normal saline is connected to a pressure transducer system. A three-ring hand-piece of a 10-mL control syringe is mounted on the blood gas syringe and placed between the thumb, index finger, and middle finger. Velcro bands are glued to the half-cut rings to fit different-sized fingers.

Force displacement of the adductor pollicis muscle is transmitted to a 3-mL plastic blood gas syringe (pulsator R, Concord Laboratories, Keene, N.H.) mounted with the three-ring hand-piece of a 10-mL Control Syringe (Becton Dickinson, Rutherford, N.J.) (Figure 1). To secure its placement between the thumb, index, and middle fingers, the rings of the hand-piece may be partially cut and straps of Velcro or elastic band may be glued or taped to achieve a better fit for different sizes. The fluid-filled syringe is connected to a monitor via a standard transducer system.

On stimulation of the ulnar nerve, muscle contraction may be observed on the monitor screen or registered on standard strip-chart paper (Figure 2), thereby facilitating the measurement of the T4/T1 ratio in the train-of-four.

In our department we have used this neuromuscular function monitoring device during hundreds of general anesthesia cases, particularly when access to the patient's head or arms is difficult. We noticed that with multiple measurement and a slight change in the position of the syringe, the tracing may not return to baseline, which

Figure 2. Force displacement of the adductor pollicis is transmitted to a monitor and registered on standard strip-chart paper.



necessitates re-zeroing of the pressurized system. This precludes the assessment of the initial simple twitch height, but the T4/T1 ratio remains unchanged, which constitutes a more accurate and reproducible measure of the degree of the neuromuscular blockade.

E. Alan Moretti, MD
Ronald Cardoso, MD
Mehrdad Rafizadeh, MD
Robert Ciolino, MD
Department of Anesthesiology
Saint Barnabas Medical Center
Old Short Hills Road
Livingston, NJ 07039

References

1. Beemer GH, Cass NM. Monitoring the neuromuscular junction. Anaesth Intensive Care 1988;16:62–6.
2. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–49.
3. Viby-Mogenson J. Clinical assessment of neuromuscular transmission. Br J Anaesth 1982;54:209–23.

Just the Fax, Ma'am

Key Words: ANESTHESIA, PREOPERATIVE EVALUATION.

To the Editor:

Anesthesiologists who practice at referral centers are at a disadvantage trying to obtain meaningful data from medical records when their patients are referred from elsewhere. Frequently, complicated patients arrive without even a written summary of any evaluation.

We describe a recent situation in which a facsimile ("fax") machine was used to determine the advisability of surgical intervention in one patient.

A 77-yr-old woman was referred to our center for laryngoscopy, bronchoscopy, and esophagoscopy because esophageal obstruction had developed 3.5 wk after resection of a Zenker's diverticulum elsewhere. She had no history of cardiovascular disease. Physical examination revealed an anxious woman apparently in her 70s, with blood pressure of 170/120 mm Hg and heart rate of 80 beats/min, who was otherwise unremarkable. Electrocardiogram showed 3-mm Q-waves in leads II, III, and aVF, but it was otherwise unremarkable.

We asked two records department staffers at referring hospitals to "fax" all old electrocardiograms from the patient's records. We determined that changes indicative of an inferior myocardial infarction had occurred sometime from 2 to 15 mo before admission. Consultant cardiologists believed that the 2-mo-old electrocardiogram displayed changes in anterior leads that strongly suggested acute infarction. The procedure was postponed and the patient was referred for further evaluation and treatment of hypertension and coronary artery disease.

Delaying elective surgery after myocardial infarction may significantly reduce the incidence of perioperative reinfarction (1–4) and the tremendous morbidity and mortality associated with it. Applying the "fax," we were able to diagnose a recent, probably silent, infarction. We thus helped reduce the risk of an anesthetic for this patient.

We recommend installing a facsimile machine in a work station near the operating room for management of similar cases.

Francis X. Dillon, MD
Nancy Zinni, MD
Mary Glass, BS
Department of Anesthesia
Fesler Hall 204
Indiana University School of Medicine
1120 South Drive
Indianapolis, IN 46202-5115

References

1. Tarhan S, Moffitt E, Taylor WF, Guiliani ER. Myocardial infarction after general anesthesia. JAMA 1972;220:1451–4.
2. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. JAMA 1978;239:2566–70.
3. Rao TK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 1983;59:499–505.
4. Shah KB, Kleinman BS, Sami H, et al. Reevaluation of perioperative myocardial infarction in patients with prior myocardial infarction undergoing noncardiac operations. Anesth Analg 1990;71:231–5.

A Safer Continuous Lumbar Plexus Block Technique?

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—lumbar plexus block.

To the Editor:

I read with interest the case report by Ben-David and colleagues in which they describe a "continuous" lumbar plexus nerve block (1). The authors used a unique sheathed needle system and nerve stimulator to locate the nerves of the lumbar plexus and to place a catheter into the "psoas compartment" (a potential space between the quadratus lumborum and psoas muscles; see Figure 1). A local anesthetic solution was intermittently injected through the catheter to provide surgical anesthesia and postoperative analgesia. A posterior paravertebral approach similar to the single injection techniques described by Chayen and Parkinson was used (2,3).

A catheter technique for lumbar plexus block was first described by Brands and Callanan (4). Local anesthetics were injected intermittently to supplement general anesthesia and to provide postoperative analgesia. We modified the Brands technique to provide postoperative analgesia after hip and knee surgery (5,6). Our initial management was similar to that described by Ben-David et al. placement of the catheter followed by intermittent injections of an amide-type local anesthetic. Our technique has, however, undergone evolution during the past 2 yr (approximately 150 nerve blocks), and we wish to report the change in our practice.

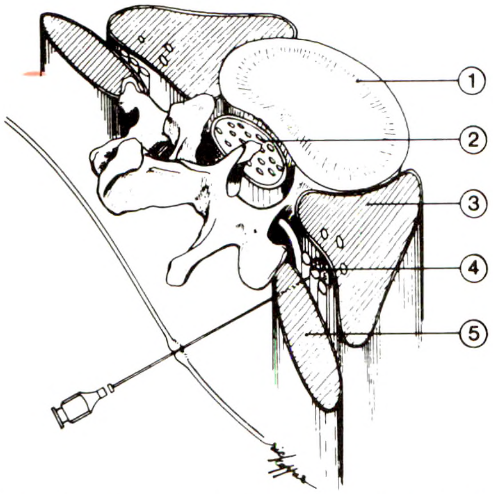


Figure 1. Lumbar plexus block. The lumbar plexus lies between the quadratus lumborum and psoas muscles. Shown are (1) the L-5 vertebral body; (2) spinal cord; (3) psoas major muscle; (4) lumbar plexus; and (5) quadratus lumborum muscle. (Reprinted with permission from Miller RD, ed. Anesthesia. 2nd ed. Volume 2. New York: Churchill Livingstone, 1986:1037.)

We have abandoned intermittent injections of long-acting amide-type local anesthetics in favor of a continuous infusion of 1% chloroprocaine for several reasons: (a) an ester-type local anesthetic may pose a lower risk of systemic toxicity because it is rapidly metabolized in the plasma; (b) the high peak plasma concentrations attained after intermittent boluses of local anesthetic (and attendant risk of toxicity) are avoided; (c) continuous infusion of local anesthetic provides continuous analgesia; and (d) use of a short-acting local anesthetic permits quick reversal of drug effect should neurologic examination of the extremity be required.

Minimizing the risk of systemic local anesthetic toxicity is particularly important if the catheters are "topped up" in unmonitored patient rooms. Ben-David and associates warn that "only qualified personnel [should] inject local anesthetic solution into the catheter" (1). Although the risk of toxicity is not eliminated by our technique, I believe that it is much less likely to occur. In addition to the safety advantages, our technique provides continuous patient comfort and may extend the theoretical advantages of regional sympathectomy into the postoperative period.

George W. Rung, MD
Department of Anesthesia
Pennsylvania State University College of Medicine
P.O. Box 850
Hershey, PA 17033

References

1. Ben-David B, Lee E, Croitoru M. Psoas block for surgical repair of hip fracture: a case report and description of a catheter technique. Anesth Analg 1990;71:298–301.
2. Chayen D, Nathan H, Chayen M. The psoas compartment block. Anesthesiology 1976;45:95–9.
3. Parkinson SK, Mueller JB, Little WL, Bailey SL. Extent of blockade with various approaches to the lumbar plexus. Anesth Analg 1989;68:243–8.
4. Brands E, Callanan VI. Continuous lumbar plexus block-analgesia for femoral neck fractures. Anaesth Intensive Care 1978;6:256–8.
5. Rung GW, Hanks GA, Kalenak A, Satterfield J. Continuous lumbar plexus blockade after anterior cruciate ligament repair. Reg Anesth 1990;15:S53.
6. Rung GW, Marshall WK. Nerve blocks in the critical care environment. Crit Care Clin 1990;6:343–67.

Single-Bolus Injection of Esmolol for Treatment of Intraoperative Tachycardia

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol.

To the Editor:

The use of a single intravenous (IV) injection of esmolol (50, 80, and 100 mg) has recently been described by Gold et al. to treat intraoperative tachycardia (1,2). We present a case of severe bradycardia and hypotension secondary to a single-bolus IV injection of esmolol (20 mg) during maintenance of anesthesia. A 69-yr-old, 68-kg woman was scheduled for elective surgery. The preoperative evaluation was unremarkable. The electrocardiogram showed normal sinus rhythm and a preinduction heart rate of 85 beats/min. Thiopental, 4 mg/kg IV, was used for induction of anesthesia with 0.1 mg/kg IV vecuronium to facilitate tracheal intubation. Anesthesia was maintained with oxygen and isoflurane at 1.5% end-tidal concentrations. About 10 min after induction and intubation, the patient developed a tachycardia at 120 beats/min for more than 10 min, with a blood pressure of 160/80 mm Hg. Esmolol, 20 mg (0.29 mg/kg) IV, was administered for treatment. The heart rate decreased to 40 beats/min, and blood pressure decreased to 85/50 mm Hg. The concentration of isoflurane was reduced, and within 5 min the heart rate had returned to 85 beats/min and blood pressure to 115/70 mm Hg. No ischemic changes were seen on the electrocardiogram, and postoperative electrocardiogram and neurologic examination were unremarkable.

The dosage of esmolol recommended by the Food and Drug Administration for treatment of tachycardia in nonanesthetized patients is 0.5 mg/kg IV over 1 min. This may be excessive in anesthetized patients. The incidence of symptomatic hypotension and bradycardia in awake patients has been reported to be as high as 13% with this dosage. The dose we used, 20 mg, is considerably less than the dose recommended by the studies by Gold et al. The authors reported a mean 20%–24% decrease in heart rate in both studies, but individual patients may have had a greater response than was apparent from the group data. Blood pressure was reported as not a problem in their studies. Our patient had a 67% reduction in heart rate and a 40% reduction in blood pressure. The possible reasons for this profound response are multiple, but there was no evidence of hypoxemia, hypercarbia, or hyperkalemia on blood gas analysis. Pulse oximetry and end-tidal carbon dioxide had been in the expected range. Our patient showed no clinical evidence of hypovolemia during the perioperative course. The vial and syringe were rechecked for correctness of dosage and content. The study by Gold et al. used nitrous oxide, oxygen, and isoflurane. Vecuronium was used if muscle relaxation was needed after intubation. Our patient was intubated, and anesthesia had been maintained for over 10 min with isoflurane with a heart rate >95 beats/min (≥20% of baseline) and a systolic blood pressure >140 mm Hg.

The dose and techniques recommended by Gold et al. may be excessive when used for the treatment of intraoperative tachycardia during maintenance of anesthesia in some patients, perhaps especially in the elderly. Personal experience in 12 anesthetized patients (ages 23–79 yr) has demonstrated that a much lower initial dose, i.e., 0.15 mg/kg (approximately 10 mg/70 kg) IV, is often adequate. If tachycardia persists, the same dose is repeated in 60 s. This technique allows rapid control and the convenience of bolus injection and may avoid profound bradycardia and hypotension.

Steven R. Ford, MD
Department of Anesthesiology, E-91
University of Texas Medical Branch
Galveston, TX 77550-2778

References

1. Gold MI, Sacks DJ, Grosnoff DB, Herrington C, Skillman CA. Use of esmolol during anesthesia to treat tachycardia and hypertension. Anesth Analg 1989;68:101–4.
2. Gold MI, Whirley J, Jacque J. Treatment of intraoperative tachycardia with a single bolus of esmolol. Anesthesiology 1989;71:A17.

Insulated Circuit Hose Improves Heated Humidifier Performance in Anesthesia Ventilation Circuits

Key Words: HUMIDIFICATION, INSULATED CIRCUIT HOSES. EQUIPMENT, INSULATED CIRCUIT HOSES.

To the Editor:

Tracheal intubation bypasses the upper airway, and, unless inspired gases are heated and humidified, complications such as heat loss, impaired mucociliary function, and damage to ciliated epithelium may result (1–3). To alleviate these complications, heated humidifiers have been employed in breathing circuits. We have observed that much of the heat and humidity provided is lost from the circuit hoses as the gases are conducted to the patient. This creates a large thermal gradient between the humidifying unit and the circuit Y-piece such that the humidifier unit is incapable of delivering gases to the patient at the selected temperature (37°–40°C) despite hazardously high water bath temperatures (up to 85°C). To reduce the thermal gradient, we constructed an insulated ventilation circuit hose by wrapping a 48-in corrugated polypropylene ventilation hose (Item #908606, Dryden Corporation, Indianapolis, Ind.) with 4-in orthopedic cast padding (Figure 1).

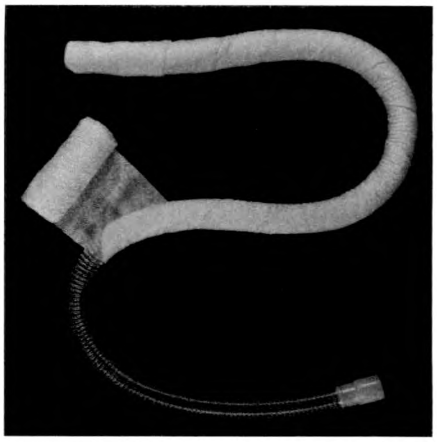


Figure 1. Forty-eight-inch polypropylene ventilation hose thermally insulated with orthopedic cast padding.

To test the improved hose, we incorporated it into the inspiratory limb of a semiclosed circle circuit (Narkomed II, North American Drager, Telford, Pa.) equipped with a servo-controlled heated chamber humidifier (model MR450, Fischer and Paykel, Pharmaseal Co., Valencia, Calif.). A 2-L ventilation bag was attached to the circuit Y-piece to take the place of a patient. The servo temperature sensor and a recording thermometer were placed at the patient Y-piece. With all circuit and humidifier components at room temperature, the humidifier was turned on and the servo temperature control was set at either 37.0 or 40.0°C. Ventilation (fresh gas flow = 1 L/min, rate = 7 breaths/min, tidal volume = 1.0 L) and recording of temperatures were initiated and continued until the gas temperature at the Y-piece remained stable (±0.2°C) for a period of 20 min (plateau temperature). Five trials were performed at each temperature setting (37.0 and 40.0°C) for the insulated and uninsulated ventilation hoses. Plateau temperature and rate of gas temperature rise were analyzed using unpaired two-tailed *t*-analysis with $P < 0.05$ considered to be significant.

There were no significant differences between room or starting humidifier bath/airway temperatures. The temperature of the Y-piece gas in the uninsulated inspiratory limb circuit *never* achieved the target temperature set on the servo heater unit (37.0 or 40.0°C) as the mean plateau temperatures achieved were 32.4 ± 0.9°C (SD) and 32.7 ± 1.0°C, respectively. With the insulated inspiratory limb hose, gas temperatures at the Y-piece consistently attained and plateaued within ±0.2°C of the servo heater unit temperature setting (37.1 ± 0.2°C and 40.0 ± 0.1°C, respectively). Additionally, the time required to reach plateau temperature was significantly less (~35%, $P < 0.05$) at both the 37.0 and 40.0°C settings.

The current remedy to the problem of circuit hose heat loss has been the addition of servo-controlled heated wires within the ventilation tubing (4). This requires a complex and expensive humidifier heater unit ($1400 for a unit with heated wire capability vs $600 for one without [5]) as well as cleaning and disinfection of the nondisposable ($50 per set) heating wires. The cost of the disposable orthopedic felt to insulate one 48-in ventilation hose is approximately $0.50.

The insulated ventilation hose economically improves the performance of the servo-controlled heated humidifier as evidenced by the rapid achievement and stable maintenance of set temperature. We recommend that the inspiratory limb ventilation hose be insulated whenever a servo-controlled flow-over heated humidifier is used.

Alan R. Mizutani, MD
George Ozaki, AS
Ronald Rusk, AS
Department of Anesthesiology
University of California, San Diego Medical Center
San Diego, CA 92103

References

1. Stone DR, Downs JB, Paul WL, Perkins HM. Adult body temperature and heated humidification of anesthetic gases during general anesthesia. Anesth Analg 1981;60:736–41.
2. Gray TD, Benson DW. Systemic and pulmonary changes with inhaled humid atmosphere: clinical applications. Anesthesiology 1969;30:199–207.
3. Chalon J, Loew DAY, Malebranche J. Effects of dry anesthetic gases on tracheobronchial ciliated epithelium. Anesthesiology 1972;37:338–43.
4. Evaluation: heated humidifiers. Health Devices 1987;16:223–50.
5. 1990 Catalogue. Huntington Beach, Calif.: Gary Hull Anesthesia, Inc.

Leakage of Anesthetic Agent From an Ohmeda Tech IV Vaporizer

Key Words: EQUIPMENT, VAPORIZERS.

To the Editor:

On many occasions, we have observed leakage of anesthetic agent from the drain port of the Ohmeda Tech 4 vaporizer. Apparently, these leaks have been caused by inadvertent loosening of the drain plug (a screw that fits snugly into the drain, Figure 1) as the filler cap is being removed to allow addition of anesthetic to the vaporizer; only a few degrees rotation of the plug can lead to a loss of liquid agent.

Usually, the problem manifests as a slow drop-by-drop leak of agent onto the anesthesia machine table top. However, the agent may also be emitted as a spray when the vaporizer is turned on. Obvious adverse consequences of such leaks include unnecessary exposure of personnel to anesthetic vapors, loss of expensive agent, unanticipated loss of anesthetic from the vaporizer, and damage to items on the table top.

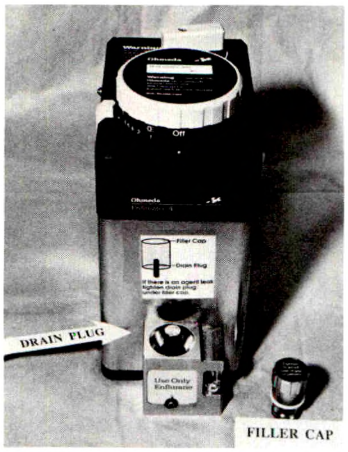


Figure 1. Ohmeda Tech IV Vaporizer with filler cap removed to show drain plug.

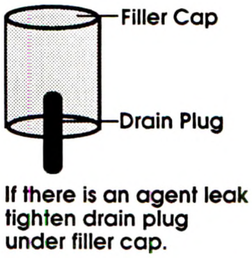


Figure 2. Precautionary label for Ohmeda Tech IV Vaporizer.

Thus, we have placed precautionary labels (Figures 1 and 2) prominently on our Ohmeda Tech 4 vaporizers to alert the user to this potential problem.

Donald B. Goldman, BS
Phillip S. Mushlin, MD, PhD
Department of Anesthesia
Harvard Medical School
Brigham and Women's Hospital
Boston, MA 02115

Book Reviews

Treatment of Chronic Pain: Possibilities, Limitations and Long-Term Follow-up

M. Mumenthaler, P. A. Van Zwieten, and J. M. Farcot, eds. New York: Harwood Academic Publishers, 1990, 337 pp, $56.00.

The last 18 months have witnessed the publication of many texts on the subject of pain management. These texts have explored the indications and applications of a variety of pain management techniques with less than 10% of the text devoted to the side effects, complications, and long-term results of the pain management techniques they discussed. *Treatment of Chronic Pain: Possibilities, Limitations and Long-Term Follow-up* is the first text to focus on these often underemphasized pitfalls. The text is edited by a multidisciplinary team consisting of an anesthesiologist, a neurologist, and a pharmacologist.

The first two sections address the side effects and limitations, as well as the long-term follow-up, of the pharmacologic management of headaches and painful peripheral neuropathies. Section 3 provides an excellent review of such topics as the adverse renal effects of nonopiate analgesics, long-term side effects of nonsteroidal antiinflammatory drugs, immediate and delayed risks of intraarticular steroids, and the use of steroids in postherpetic neuralgia.

Section 4 reviews the adverse effects of psychotropic drugs commonly used in pain management. The side effects of the minor and major tranquilizers, as well as antidepressants, are discussed. An interesting chapter on the chronopharmacology and chronotherapy of antidepressant and antiepileptic drugs is presented.

Section 5 addresses the less common side effects of neural blockade, including nerve injury and complications following neurolytic sympathetic block, and section 6 covers the behavioral modalities commonly employed in pain management, including chemical dependence as well as the limitations of behavioral techniques, hypnosis, and biofeedback. An interesting philosophical chapter on the application of the bio-psychosocial model to chronic pain nicely rounds out this section.

Section 7 discusses neurostimulation with an excellent chapter on the long-term follow-up of a large number of patients who have been treated with deep brain and spinal cord stimulation. The final chapter of section 7 provides a concise review of the mechanisms responsible for the adverse effects of neurostimulation.

Section 8 addresses the role and limitation of the neurosurgical treatment of pain and section 9 covers the role of systemic, spinal, and ventricular opioids in the management of pain. An excellent overview of the complications, failures, and pitfalls of long-term spinal morphine is given.

Although not comprehensive in scope, this text certainly addresses most of the common adverse effects encountered in the multidisciplinary practice of pain management. The emphasis on complications as well as controlled long-term follow-up makes this text useful to the clinician who would like to make more informed decisions regarding the risk-to-benefit ratio of a given pain management modality.

Steven D. Waldman, MD
*Pain Consortium of Greater Kansas City
Leawood, Kansas*

Clinical Neuroanesthesia

R. F. Cucchiara and J. D. Michenfelder, eds. New York: Churchill Livingstone, 1990, 555 pp, $79.00.

This book is a comprehensive textbook on neuroanesthesia that focuses on anesthetic techniques used at the Mayo Clinic, with which the editors and contributors have all had an association. Despite this bias, the book is comprehensive rather than parochial.

The book is divided into two sections. The first, "Scientific Foundation," includes chapters on cerebral blood flow and metabolism, cerebral spinal fluid dynamics, intercranial pressure, electrophysiologic neurologic monitoring, and cerebral protection. The chapters on cerebral blood flow metabolism and cerebral spinal fluid dynamics are unusually good and the chapter on cerebral protection is an outstanding and comprehensive synthesis of current concepts of brain metabolism and damage. The chapter on electrophysiologic monitoring suffers from a bias toward analogue electroencephalogram recording and provides minimal information about the use of the processed electroencephalogram.

The clinical chapters, in contrast to the scientific chapters, are more variable in quality and utility. Some chapters are excessively vague, and although they contain a discussion of the issues, it would be difficult for the inexperienced

©1991 by the International Anesthesia Research Society

anesthesiologist to design and conduct an anesthetic based on the information provided. Excellent chapters in this section include the discussion on ischemic cerebral vascular disease and on coma and brain death. The chapter on seizure surgery is excessively oriented toward operative technique, as is the chapter on stereotactic surgery. Several chapters seem out of place in a book on neuroanesthesia, including the chapter on neuromuscular disorders and muscle relaxants and the chapter on acute and chronic pain.

In general, this book is well-written though loosely edited. Chapter order appears to be arbitrary. There is a significant degree of redundancy. However, one benefit of this is that the clinical chapters can be read with minimal reference to the more basic material.

Despite these criticisms, this is a good first edition. Many of the authors are leaders in their respective fields. This book is highly recommended to residents and practitioners interested in neuroanesthesia, and many of the chapters may help form the knowledge base for further advances in this subspecialty.

David S. Smith, MD, PhD
Department of Anesthesiology
University of Pennsylvania
Philadelphia, Pennsylvania

Hemorrhagic Disorders Anesthesiology Clinics of North America, Volume 8, No. 3, 1990

Bruce D. Spiess, ed. Philadelphia: W.B. Saunders Co., 1990, 189 pp, $69 (annual subscription for four issues).

This volume might more appropriately be titled *Transfusion Medicine in the Operating Room* because it covers a much broader subject than just hemorrhagic disorders and yet does not specifically discuss many hemorrhagic disorders such as hemophilia or pregnancy-induced hypertension. I considered several practical questions that have been asked recently in my anesthesia practice and sought answers in this multiauthored series of review articles edited by Bruce D. Spiess.

- "What do I need to know about the physiology of anemia as I allow the patient to become more anemic intraoperatively?" Dr. Kenneth J. Tuman provides a very succinct and useful discussion of the physiology of anemia. He reviews the level of oxygen delivery where oxygen consumption becomes supply-dependent, a relationship termed the critical Do_2. Although critical Do_2 is the same whether hypoxic, stagnant, or anemic hypoxia is used to reduce oxygen delivery, the measured mixed venous pressure of oxygen varies significantly in the three states. This concept was intriguing to me, and the ensuing discussion of using Pvo_2 to determine transfusion needs will make most anesthesiologists reconsider uses of pulmonary artery saturation to determine the need for red cells.
- "Should I buy a device that measures whole blood clot strength (viscoelastic test)?" Dr. Spiess writes that the thromboelastograph is "a most valuable tool for intraoperative coagulation monitoring and management." Although I believe Dr. Spiess is confident of his conclusion, his article fails to convince me of the usefulness of this test. He does, however, provide references that may provide more persuasive material on this issue.
- "What do I do about all the abnormal PTTs that my surgical colleagues want to draw but do not want to evaluate further?" Dr. Spiess writes that a screening PTT will do very little preoperatively to predict intraoperative bleeding. He also notes that there are no studies that directly correlate abnormal PT and PTTs with the quantity of surgical blood loss. In comparison, the latest edition of Miller's *Anesthesia* has a large table that graphically and comprehensively indicates the futility of preoperative PTT monitoring and supplies the anesthesiologist with information necessary to medical practice in this area (1).
- Fluosol DA, a perfluorochemical emulsion, has not arrived in clinical practice. Will other compounds be as clinically acceptable as oxygen carriers? Dr. Gerald S. Moss and colleagues provide an intriguing review of stroma-free hemoglobin and include discussion of attempts at polymerizing hemoglobin to reduce colloid osmotic pressure. It is reassuring, as in the case with Jehovah's Witness patients, that the medical communities are making an effort to find an alternative to blood products.

In addition, this volume has very useful chapters on acute intraoperative hemodilution, perioperative blood salvage, and autologous transfusion. The final chapter brings together the three National Institutes of Health consensus development conferences on transfusion medicine and provides the best available recommendations on the appropriate use of the most commonly requested blood products. If another edition is planned, I would encourage the editors to make more use of tables, graphs, and other visual displays to aid in understanding and retention.

I would strongly recommend this volume to educators and trainees as a source material for discussions of transfusion medicine. Practitioners would find that several of the chapters mentioned above contain information useful to their practice. Dr. Spiess is successful in presenting information regarding the science, motivations, and clinical growth of operative blood transfusion medicine.

Carter P. Dodge, MD
Dartmouth Medical School
Hanover, New Hampshire

Reference

1. Roizen MF. Preoperative evaluation. In Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1990:761.

The ICU Book

Paul L. Marino. Philadelphia: Lea & Febiger, 1991, 713 pp, $39.50.

This is a different sort of ICU text that occupies a special niche somewhere between the cookbook approach of the various "pocket" manuals and the weightiness of the standard multiauthored text. Most practitioners outgrow the "cookbooks" by the end of residency and rely on original source material or general medical and surgical textbooks rather than ICU texts when confronted by the unusual patient in the intensive care unit. *The ICU Book* is not a catalog of ICU problems but rather a pattern book to aid problem solving.

The author focuses on the fundamental principles of critical illness rather than the subspecialty issues particular to a medical, neurosurgical, or coronary ICU. When looking for the scientific basis behind what have become empiric decisions in ICU care, one must search a great deal. This book, particularly in the first three chapters, brings together the fundamentals in a cohesive manner in well-chosen figures and tables.

The writing style is lively and identifies the author as someone who actually practices ICU medicine rather than observes it academically. References are current (typically 1983–1989) and reflect up-to-date concepts. The author is not afraid to take a firm stand on controversial issues but provides sufficient referenced discussion where appropriate. A computer program for generating a hemodynamic profile is thoughtfully provided for the benefit of those lacking new-generation bedside monitors with this capability. The extensive appendices (reminiscent of "peripheral brain" books carried by housestaff) supply concise and relevant information on such topics as brain death, composition of crystalloid fluids, Apache-II scoring, and acute management of cardiac dysrhythmias without taking up valuable space in a wordy discussion. The book has the information the anesthesiologist practicing critical care may need at 3 AM, and presents it concisely.

My criticisms of this text are few. Typographical errors are at a minimum, and the editing and graphic layout are superb. One major weakness is that short shrift is given to the topics of sedation and neuromuscular blockade. Succinylcholine is appropriately discouraged for prolonged ICU use, but the reason implied is hyperkalemia rather than phase II block. The author is far more enthusiastic than many in recommending haloperidol as a preferred anxiolytic. The section on central venous access mentions only two approaches to placement of an internal jugular catheter, and the chapter on arterial pressure monitoring should mention brachial artery catheters. The chapter on acute heart failure would benefit from the addition of a discussion of "bridge to transplant" using the centrifugal ventricular assist devices that are in use in many centers.

In summary, *The ICU Book* is a single handy source for basic science and physiologic concepts needed for day-to-day ICU care. For the practicing anesthesiologist with ICU responsibilities but without consultative help, this can be your pocket mentor. If you are a mentor, this book provides a useful review and a source of inspiration for bedside teaching. If you are a mentor-in-training, you may want this book as defense against tough questions from your attending. (Example: What's the correction for barometric pressure when calculating Aa gradient in a mechanically ventilated patient? Answer on page 30.) Overall, this book is a good value for those seeking to apply science to ICU routine and can be recommended to the critical care specialist and nonspecialist alike.

Thomas L. Higgins, MD
Cardiothoracic ICU
Cleveland Clinic
Cleveland, Ohio

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Baue AE. *Multiple Organ Failure. Patient Care and Prevention.* St. Louis: Mosby Year Book, 1990, 561 pp, $79.00.

Frost EAM, ed. *Preanesthetic Assessment.* Anesthesia Clinics of North America. Volume 8, No. 4. Philadelphia: W.B. Saunders, 1990, 282 pp, $69.00 annual subscription for four issues or $28.00 per single issue.

Grossman W, Baim DS, eds. *Cardiac Catheterizations, Angiography, and Intervention.* 4th ed. Philadelphia: Lea & Febiger, 1991, 698 pp, $59.50.

Rossi EC, Simon TL, Moss GS, eds. *Principles of Transfusion Medicine.* Baltimore: Williams & Wilkins, 1991, 791 pp, $95.00.

Stoelting RK, Barash PG, Gallagher TJ, eds. *Advances in Anesthesia.* Volume 8. St. Louis: Mosby Year Book, 1991, 341 pp, $59.95.

Tobin MJ, ed. *Respiratory Muscles.* Volume 3, No. 3 in Problems in Respiratory Care Series. Philadelphia: J.B. Lippincott, 1990, 289 pp, $27.00 single issue or $60.00 subscription for four issues.

A Guide for Authors

Manuscripts should be sent to:

Ronald D. Miller, MD
Editor-in-Chief
Anesthesia and Analgesia
3497 Sacramento Street
San Francisco, CA 94118

Editorial Policies

Anesthesia and Analgesia, the oldest publication for the specialty of anesthesiology, is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor.

All papers are reviewed by three or more referees. Acceptance is based on significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that includes a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *The New England Journal of Medicine* 1991;324:424–8.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

General

- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
- ☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
- ☐ Technical communications are papers that deal with instrumentation and analytic techniques.
- ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.
- ☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double-spaced, and a title and three copies must be provided.
- ☐ Type manuscripts on white bond paper, 216 by 279 mm (8½ by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in.) using double-spacing throughout.
- ☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.
- ☐ Submit three copies of the manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter and by letters granting permission to reproduce previously published materials or to use illustrations that may identify subjects.
- ☐ Authors should keep copies of everything submitted.

Title Page

- ☐ The title page should contain the title of the article, which should be concise but informative;
- ☐ A short running head of no more than 40 characters (count letters and spaces) placed at the bottom of the title page and identified;
- ☐ First name, middle initial, and last name of each author, with highest academic degree(s); each listed author must (a) have participated in the work to the extent that he or she could publicly defend its contents; (b) have read the manuscript before its submission for publication; and (c) be prepared to sign a statement to the effect that he or she has read the manuscript and agrees with its publication;
- ☐ Name of department(s) and institution(s) to which the work should be attributed;
- ☐ Disclaimers, if applicable;
- ☐ Name, address, telephone number, and FAX number of author responsible for correspondence about the manuscript;
- ☐ Name and address of author to whom requests for reprints should be addressed, or a statement that reprints will not be available from the author;
- ☐ The source(s) of support in the form of grants.

Abstract and Key Words

- ☐ The second page should carry an abstract of not more than 150 words. (Abstracts are not needed for Clinical Reports.)
- ☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.
- ☐ Define all abbreviations except those approved by the International System of Units.
- ☐ Key (indexing) words: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article.

Text

- ☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the following headings: Introduction, Methods, Results, and Discussion.
- ☐ Case reports, reviews, and editorials do not require the above sections.
- ☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references and do not review the subject extensively.
- ☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

©1991 by the International Anesthesia Research Society

☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data.

☐ *Units of measurement:* Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in **SI units** with, if desired, present conventional metric units in parentheses.

References

All references must be available to all readers. Cite only references to books and articles or abstracts published in peer-reviewed *Index Medicus* journals. Abstracts appearing only in programs of meetings are not acceptable, nor are abstracts more than five years old.

☐ Number references consecutively in the order in which they are first mentioned in the text.

☐ Identify references in text, tables, and legends by arabic numerals (in parentheses, on line)

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus.*

☐ The titles of journals must be abbreviated according to the style used in *Index Medicus.*

☐ References must be verified by the author(s) against the original documents, and the entire list must be checked for nonduplication.

Examples:

1. *Standard journal articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
   Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. Anesth Analg 1991;72:275–81.
2. *Personal author(s) of books and monographs*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974.
3. *Chapter in a book*
   Weinstein L, Swartz NM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

Tables

☐ Type each table double-spaced on a separate sheet. Do not submit tables as photographs.

☐ Number tables consecutively and supply a brief title for each. Give *each* column a short or abbreviated heading.

☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use lower-case italicized letters in alphabetical order.

☐ Do not use internal horizontal or vertical rules.

☐ Cite each table in the text in consecutive order.

☐ If data are used from another published (or unpublished) source, submit written permission from both author and publisher and acknowledge fully.

Illustrations

☐ Submit three complete sets of figures. Figures should be in black and white only and be professionally drawn and photographed; freehand or typewritten lettering is unacceptable. Note: Art work of published articles will not be returned.

☐ Send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm but no larger than 203 by 254 mm, instead of original drawings, roentgenograms, or other material.

☐ Many computer-generated figures are unsatisfactory for reproduction and should be professionally redrawn. Lettering should be of adequate size to retain clarity after reduction (*final* lettering size in print should be 1.5 mm high). Symbols, cross-hatching, and stippling within a figure should be sharp and distinct enough to retain uniqueness after reduction.

☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures. Do not mount them on cardboard or scratch them by using paper clips. Do not bend figures.

☐ Photomicrographs must have internal scale markers. Symbols, arrows, and letters used in the photomicrographs should contrast with the background.

☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from both the author and the publisher to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.

Legends for Illustrations

☐ Type legends for illustrations double-spaced starting on a separate page, with arabic numerals corresponding to the illustrations.

☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

Abbreviations

☐ At first mention in text, spell out in full and follow immediately with the abbreviation (enclosed within parentheses).

☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.

☐ Consult the following sources for abbreviations:

1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 5th ed. Bethesda, Maryland: Council of Biology Editors, 1983;
2. American Medical Association. Manual of style. 8th ed. Baltimore, Maryland: Williams & Wilkins, 1989.

Exclusive Publication Statement

☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.

☐ Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

CO-INDUCTION OF ANESTHESIA

A synergy of effects and advantages

Co-induction—when two or more agents rather than one are used for induction—may offer clinical benefits if there is anesthetic synergy. Specifically, subanesthetic doses of each agent may produce a prompt, short-acting effect with more stable hemodynamics than one agent alone.[1]

A classic example of synergy is mutual enhancement of receptor-site affinity: *e.g.,* a benzodiazepine such as VERSED may alter barbiturate receptors in a way that enhances barbiturate effects. Likewise, a barbiturate may potentiate a benzodiazepine by acting at its receptor sites.[2,3]

Lower doses of both agents

Several studies have shown that a small initial dose of VERSED will allow lower induction doses of thiopental, methohexital, fentanyl, alfentanil or ketamine.[1,4-9]

In one study of 90 unpremedicated ASA Class I & II patients, co-induction with VERSED followed by thiopental required just 1/4 of each drug's usual ED_{50}.[5]

Lower risk of breakthrough awareness

VERSED produces a marked amnestic effect. Therefore, a VERSED co-induction may reduce the possibility of recall (*e.g.,* during intubation) in the event of lightening of anesthesia with short-acting hypnotics such as thiopental or propofol.

Dosing considerations with VERSED® (midazolam HCl/Roche)Ⓒ

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.,* drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Roche Laboratories
a division of Hoffmann-La Roche Inc.

Copyright © 1991 by Hoffmann-La Roche Inc. All rights reserved.

IDEAS IN ANESTHESIA

AN ONGOING SERIES

Please see summary of product information on following page.

References: **1**. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for coinduction of thiopental anesthesia in patients. *Anesthesiology*. 1990; 73(3A):A1216. **2.** Skolnick P, *et al.* Pentobarbital: dual actions to increase brain benzodiazepine receptor affinity. *Science*. March 1981;211:1448-1450. **3.** Miller LG, *et al.* Acute barbiturate administration increases benzodiazepine receptor binding in vivo. *Psychopharmacology (Berlin)*. 1988;96:385-390. **4.** White PF. Comparative evaluation of intravenous agents for rapid sequence induction—thiopental, ketamine and midazolam. *Anesthesiology*. 1982;57:279-284. **5.** Tverskoy M, *et al.* Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg*. 1988;67:342-345. **6.** Tverskoy M, *et al.* Midazolam acts synergistically with methohexitone for induction of anaesthesia. *Br J Anaesth*. 1989;63:109-112. **7.** Kissin I, *et al.* Alfentanil potentiates midazolam-induced unconsciousness in subanalgesic doses. *Anesth Analg*. 1990;71:65-69. **8.** Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69:213-217. **9.** Ben-Shlomo I, *et al.* Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth*. 1990;64:45-47.

VERSED®
(brand of midazolam HCl/Roche)Ⓒ
INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

> Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)
>
> The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: *General:* Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

VERSED® (brand of midazolam HCl/Roche)

2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: *Respiratory:* Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. *Cardiovascular:* Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. *Gastrointestinal:* Acid taste, excessive salivation, retching. *CNS/Neuromuscular:* Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. *Special Sense:* Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. *Integumentary:* Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. *Miscellaneous:* Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (*e.g.*, sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.I. 0988

Roche Laboratories
ROCHE®
a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

Classified Advertising

FELLOWSHIP—PEDIATRIC ANESTHESIOLOGY
The Department of Anesthesiology of Columbus Children's Hospital is expanding its fellowship program. Positions are currently available for a 1-year fellowship in pediatric anesthesiology. Children's Hospital of Columbus, Ohio is a 313-bed general pediatric institution with a surgery caseload of 13,000–14,000 cases per year. All pediatric surgical specialities are represented with large case loads in pediatric neurosurgery and cardiovascular surgery. Regional anesthesia in infants and children along with acute/chronic pain management experience is available. An active transplantation service is present. Opportunity for research is provided under the guidance of a full-time director of research. Inquiries should be submitted to J. David Martino, MD, Chairman, Department of Anesthesiology, Columbus Children's Hospital, Columbus, OH 43205.
531K/D

MISSOURI
The Department of Anesthesiology of St. Louis University School of Medicine is seeking board-qualified or certified full-time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.
544L/E

MAINE
BC or BE MD to join group of three MD anesthesiologists and four CRNAs, in the practice of anesthesia, intensive care and respiratory care. Phone (207) 622-1959 from 8:30 AM to 3:30 PM. Write to Chief of Anesthesia, Kennebec Valley Medical Center, 6 East Chestnut Street, Augusta, ME 04330.
560L/E

OHIO
Anesthesiologist, University Hospitals. Must be at least board eligible. Equal opportunity affirmative action employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.
571A/F

ILLINOIS, CHICAGO
Anesthesiologist BC/BE to join expanding group practice limited to outpatient anesthesia. Excellent opportunity for growth. Send CV to Marc Sloan, MD, 25 East Washington, Suite 300, Chicago, IL 60602.
574A/F

WANTED?
Affable anesthesiologist to join progressive fun-loving department in central Vermont area. Locate in the mountains. See the leaves. 4 MD, 1 CRNA group. We do pain our way. DO IT NOW—send CV to Chairman, Department of Anesthesia, c/o Central Vermont Hospital, PO Box 547, Barre, VT 05641. A limited time offer. Respond now!!
580A/D

CALIFORNIA
The UCLA Department of Anesthesiology has openings for faculty with experience in anesthesia for organ transplantation. Requisites include clinical and teaching skills; eligibility for a California medical license; ABA certification or in process. Address correspondence with names of five references and curriculum vitae to Stuart F. Sullivan, MD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.
584A/F

THE UNIVERSITY OF NEW MEXICO
A reorganized, expanding Department of Anesthesiology in the "Land of Enchantment" has seven immediate openings at the Assistant and Associate Professor levels. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to James C. Scott, MD, Associate Professor and Acting Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106, (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.
585A/F

Cardiac anesthesiologists and Director of Obstetric Anesthesiology sought for academic medical center practice. Candidates for obstetric position must have experience in all types of obstetric anesthesia. Interest in research and teaching highly desirable. Present staff of 25 MDs, over 40 CRNAs, and over 20 residents provides challenging anesthesia care team setting. OR area contains state-of-the-art equipment in 20 new or renovated suites. Interested applicants should send CV and three references to: Dr. Philip Lumb, Professor and Chairman, Albany Medical College, Department of Anesthesiology, Code A-131, Albany, NY 12208. EOE
592B/F

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announcements, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 1/4 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost $1.25 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of $17.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia* Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

WISCONSIN

Anesthesiologist BC/BE to work with four MDs in 200+ bed hospital and surgicenter midway between Milwaukee and Chicago. Fee for service. Send CV and references to Dr. I. Romana, PO Box 594, Kenosha, WI 53141.

597B/E

INDIANA

Faculty positions are available at all academic ranks for adult anesthesia. Positions include teaching and administrative responsibilities as well as opportunities to pursue research interests. Experience in pain management and organ transplantation is desirable. All candidates must be board certified or board eligible. Individuals appointed to the tenure track will be required to maintain an active and ongoing research program. Please send curriculum vitae to Robert K. Stoelting, Professor and Chairman, Department of Anesthesia, Indiana University School of Medicine, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115. Indiana is an equal opportunity employer.

599B/D

OREGON

Fellowship—Pain Management. July 1991 and July 1992 Fellowship positions available for physicians who have completed clinical anesthesia training. Setting is a multidisciplinary pain management center that deals with the entire range of acute and chronic outpatient and inpatient pain problems. Experience offered in most diagnostic and therapeutic procedures including intraspinal narcotics and stimulators, cryo, regional blockade, PCA. An active research program exists and participation by fellow is encouraged. Please send CV and names of three references to Wendell C. Stevens, MD, Chairman, Department of Anesthesiology, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201.

600B/D

NEW HAMPSHIRE

Excellent opportunity for BC/BE anesthesiologist to join two-person group. Surgical cases include OB/GYN, urology, ENT, ophthalmology, Peds, Ortho, and vascular and general surgery. Position open due to enormous growth in surgical base. Partnership position includes competitive compensation and benefit package. NH is a tax-free state that enjoys year-round recreational and cultural opportunities. This position combines a challenging practice with a quality lifestyle that is rare in this age of corporate medicine. For additional information call or write: Martin Rosenberg, Director of Professional Services, Valley Regional Hospital, 243 Elm Street, Claremont, NH 03743; (603) 543-1606.

601B/D

DEPARTMENT OF ANESTHESIOLOGY, UNIVERSITY OF CALIFORNIA, SAN DIEGO is recruiting for five faculty positions at all ranks. One position is the Director of the UCSD Pain Management Program. Applicants for this position must have experience in all aspects of inpatient and outpatient pain management and have extensive experience in pain research and treatment. Applicants must demonstrate motivation to expand a pain management center and be able to direct a clinical pain research program involving protocol-driven human studies. The four other positions require experience in teaching and clinical training, patient care, and research interest or experience is preferred. One position requires demonstrated experience in critical care. One position requires subspecialty training and experience in obstetric anesthesia. One of the five positions may be tenured track. Otherwise the positions are non-tenured track. Rank and salary commensurate with experience and based on the UCSD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology and a California medical license is required. Possession of a certificate of special qualifications in critical care medicine or eligibility to take the qualifying exam is required for the critical care position. Please send letter, curriculum vitae, and names/addresses of three references to Harvey M. Shapiro, MD, Department of Anesthesiology, H-770-A, University of California San Diego Medical Center, 225 Dickinson Street, San Diego, CA 92103. The University of California, San Diego is an equal opportunity/AA employer. All applications received by April 30, 1991 will receive thorough consideration.

603B/D

Tertiary care hospital in Cleveland, Ohio currently seeking BC Division Director to join group of four anesthesiologists, directing nine anesthetists through a team approach. Surgical schedule includes OHS, trauma, minimal pediatrics, no OB. Send CV to Aldona T. Lyon, MD, Acting Director, Division of Anesthesiology, Saint Vincent Charity Hospital and Health Center 2351 East 22nd Street, Cleveland, OH 44115.

610CD

PLANNING TO RETIRE AND MOVE TO FLORIDA—WHY WAIT?

Established group looking for anesthesiologist who would like to spend a few practice years before retirement in a Florida Gulf Coast Outpatient Specialty Clinic supervising one CRNA. Working conditions are a relaxed and pleasant day job (no nights, weekends, holidays) with no administrating or office responsibilities. If practice hassles, high stress cases, and call responsibilities are getting to be too much, this one is for you. Area offers outstanding outdoor activities, professional sports and cultural events. Must have a Florida license. Reply to Box 612CD.

612CD

FLORIDA

Central Florida Area—Excellent opportunity for MD with fellowship or extensive clinical experience in chronic pain management. Salary to partnership. Reply Box 613C/E.

613C/E

BE/BC ANESTHESIOLOGIST

SW PA, 300-bed, modern community hospital to work with 3 MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to box 614C/F.

614C/F

MINNESOTA: MEDICAL DIRECTOR OUTPATIENT ANESTHESIA

Excellent opportunity for an experienced anesthesiologist to join a single specialty group of nine. Medical Director will assist in planning and development of new ambulatory care facility at the Saint Cloud Hospital. Saint Cloud Hospital is a 489-bed regional medical center serving an area of 440,000 Central Minnesotans. Duties will include at least 80% outpatient anesthesia. Qualifications: board certification with strong interest and experience in outpatient anesthesia. Good interpersonal and organizational skills required. This position offers a competitive salary, excellent benefits, and limited call duty. St. Cloud is a rapidly growing area of 100,000 people located 70 miles northwest of Minneapolis/St. Paul. A clean safe city, St. Cloud offers three universities, a wide variety of cultural and recreational opportunities, and an ideal family environment. Please send CV to John Schnettler, Physician Recruiter, Saint Cloud Hospital, 1406 6th Avenue North, St. Cloud, MN 56303; 1-800-289-6654.

618CD

ANESTHESIOLOGIST

Sinai Hospital, an acute-care teaching hospital, in northwestern Detroit seeks a qualified anesthesiologist who is board certified or in the exam process. Salary will be commensurate with experience. The candidate will be expected to participate actively in both undergraduate and resident education. Send CV to Mark McNash, Administrative Director, Sinai Hospital, 6767 West Outer Drive, Detroit, MI 48235. An equal opportunity employer.

620CD

FLORIDA

BC/BE Anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/H.

621C/H

PAIN FELLOWSHIP

Expanding Pain Management Center of Medical College of Georgia has opening for Pain Fellow starting July 1991. Choice of 6 or 12 months at competitive salary. Setting is interdisciplinary, with focus on return to functionality. Busy nerve block clinic, acute pain service with PCA and epidural analgesia, cancer pain management, and tertiary region-wide referral of large variety of complex diagnostic challenges. Growing pediatric pain program, including postop, oncology, and sickle cell crisis. Applicant must have completed residency training in anesthesiology, be board eligible, and have Georgia license. Clinical research encouraged. The Fellow supervises two residents plus one student; adequate management exposure to direct a pain service on completion. Augusta is a clean, pleasant university town near huge lake for boating, and a few hours from Atlanta, beach, and mountains.

Inquires to Rudolph H. de Jong, MD, (404) 721-PAIN, application packet from Susan W. Dawkins, Department of Anesthesiology, Medical College of Georgia, Augusta, GA 30912-2700. EEO/AA Employer.

622CD

PENNSYLVANIA

Immediate opening for BC/BE anesthesiologist to join 2 MDs and CRNAs in PA. Fee for service. Call Dr. Shah, (717) 242-7186, 9 AM to 5 PM.

623CD

ILLINOIS

Anesthesiologist to join congenial group of MDs/CRNAs expanding to provide anesthesia coverage for only hospital in city since recent merger. No open heart or neurosurgery. Environment conducive to family living, variety of schools, recreation. Good opportunity with stable future. City located in east central Illinois with population of approx. 40,000 (35 mile radius service area with 126,126 population). Within driving distance of Chicago and Indianapolis. Please send CV to Box 624C/H.

624C/H

ALABAMA—ANESTHESIOLOGIST

Faculty position for clinical BC/BE anesthesiologist at University of Alabama at Birmingham, Department of Anesthesiology. Opportunities to do clinical research, variety of clinical cases including liver transplantation. Desire to participate in teaching necessary. Limited night call. Generous benefit package. Salary competitive with private practice situations. Located in downtown Birmingham; city rated "America's most livable city" by U.S. Conference of Mayors, June 1989, and rated by *Newsweek*, February 1989, as "one of the nation's top 10 hot cities." Please contact Simon Gelman, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of Alabama at Birmingham, 619 South 19th Street, Birmingham, AL 35233, (205)934-4696. An Affirmative Action/Equal Employment Opportunity Employer.

626C/F

DIRECTOR, PAIN MANAGEMENT SERVICE

The Department of Anesthesiology at the Oregon Health Sciences University is recruiting for a Director of our Pain Management Service. The Service encompasses management of acute and chronic pain, training of medical students, residents, and fellows and research. The Service provides a multidisciplinary approach to pain control and has vigorous clinical psychology and neuroimplant components. Excellent interdisciplinary relationships exist with neurosurgery, orthopedics, and surgical oncology. Board eligibility in anesthesiology or equivalent certification plus training and/or experience in pain management are required. Research experience and evidence of productivity are desired. Academic rank for successful candidate will be determined by qualifications. Candidate must be eligible for Oregon medical license.

Please send curriculum vitae and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, OHSU, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an equal opportunity/affirmative action employer.

627C/E

FULL-TIME ANESTHESIOLOGIST

BC or BE to join a group of anesthesiologists and CRNAs providing all types anesthesia coverage, though little obstetrical, to three hospitals and a day surgery facility in a southwest Louisiana city of approximately 75,000. Please send CV to Lake Charles Anesthesiology, 1415 18th Street, Lake Charles, LA 70601.

634C/H

ANESTHESIOLOGY CA-4 CRITICAL CARE MEDICINE

CA-4 training in Critical Care Medicine satisfying the requirement for certification of specialty competence in critical care medicine through anesthesiology. Newly approved program at the Albany Medical Center. Two positions available for July 1991. Send CV to Carol Kiner/Albany Medical Center/Anesthesia A-131/Albany, NY 12208.

631D/G

YALE UNIVERSITY SCHOOL OF MEDICINE: DEPARTMENT OF ANESTHESIOLOGY

From time to time, faculty positions are available for both clinical anesthesiologists and research staff. These appointments are for immediate and future placement. Please respond prior to May 31, 1991 by sending your CV to Paul G. Barash, MD, Chairman, Department of Anesthesiology, Yale University School of Medicine, PO Box 3333, New Haven, CT 06510. Yale is an Affirmative Action Employer and provides equal opportunities for employment to all applicants.

632D

ANESTHESIOLOGIST

Board certified/eligible to join expanding small group practice. Experienced in all anesthesia techniques including epidural block and pain management. No open heart or neurosurgery. Good opportunity for growth. Please send CV to Mount Vernon Anesthesia Associates, Box 391, Mount Vernon, OH 43050.

633D/F

NORTHERN NEW ENGLAND

Chief and/or Staff Anesthesiologist, BC/BE for 194-bed VA Medical Center, fully affiliated with Dartmouth-Hitchcock Medical Center and Dartmouth Medical School. Active teaching hospital. Academic appointment and salary commensurate with experience. Part-time position a possibility. Good schools, cultural offerings, beautiful country environment, good skiing, excellent book store. Two and a half hours from Boston, Massachusetts—one and a half hours from Burlington, Vermont. For further information, call John M. Head, MD, Chief of Surgery, or Susanne Learmonth, Acting Chief of Anesthesia, (802) 295-9363, extension 5290, or FTS 834-1290, or send CV to above at VA Medical Center, White River Junction, VT 05001. EOE/MF.

635D/F

PEDIATRIC ANESTHESIA

Due to expansion of our clinical responsibilities, positions are available for pediatric anesthesiologists at Arkansas Children's Hospital. We provide primary and tertiary care for children locally and in six surrounding states. We are especially interested in those with special training or experience in pediatric cardiovascular anesthesia and pain management. Please send replies to Raeford E. Brown, Jr., MD, Chief, Division of Pediatric Anesthesia, Arkansas Children's Hospital, 800 Marshall Street, Little Rock, AR 72202-3591. An equal opportunity employer.

636D/F

PEDIATRIC ANESTHESIOLOGIST/ INTENSIVIST

The Department of Anesthesiology at Duke University Medical Center is seeking a board-certified/board-eligible anesthesiologist to join the faculty. Applicants should have formal training beyond the 3 year continuum in the subspecialties of pediatric anesthesia and/or critical care or have recognized skills in lieu of normal fellowship training. Faculty candidates must have a strong desire to conduct clinical research and teaching, in addition to clinical expertise. Academic title and compensation consistent with experience. send curriculum vitae to Dr. J.G. Reves, MD, Interim Chairman, Department of Anesthesiology, P.O. Box 3094, Duke University Medical Center, Durham, NC 27710. Duke University is an EO/AA employer.

637D

PEDIATRIC ANESTHESIOLOGIST WANTED: N.Y.C. suburb, 2 years to partnership. Reply to Box 638D.

638D

DEPARTMENT OF ANESTHESIOLOGY UNIVERSITY OF MINNESOTA

The University of Minnesota, Department of Anesthesiology, is seeking three academic anesthesiologists for full-time faculty positions. Positions will be at the rank of Assistant Professor, tenure track, Associate Professor with tenure, or Professor with tenure, depending on experience and qualifications. Responsibilities will include the teaching of medical students, residents and fellows, the supervision of clinical cases, and administrative duties within the department. Candidates must be prepared to undertake clinical and/or laboratory research.

Candidates must have an MD degree and four years of post MD training.

To be eligible for the rank of Assistant Professor on tenure track, candidates must have demonstrated involvement in quality research and competence in teaching.

To be eligible for the rank of Associate Professor with tenure, candidates must have demonstrated distinction in research and writing as well as effectiveness in teaching.

To be eligible for the rank of Professor with tenure, candidates must have the above, plus a national reputation in research and evidence of leadership in the applicants' professional field.

Any area of subspeciality is of interest, although specific needs exist in acute and chronic pain management, regional anesthesia, and cardiac, neurosurgical, and transplantation anesthesia.

A generous compensation and benefit package is available.

Last date for receipt of applications is April 30, 1991, with beginning date to be negotiated. Send letters of application with the names of three references and curriculum vitae to Chairman, Search Committee, Department of Anesthesiology, University of Minnesota, 420 Delaware Street SE, Minneapolis, MN 55455.

The University of Minnesota is an equal opportunity educator and employer.

639D

STAFF MDA

Need ASAP or 7/91. Midwest Metro, 399 beds, BE/BC. Includes heart-OB-pain. Relaxed, excellent work/living environment. Send CV to A.M.I., P.O. Box 2153, Shawnee Mission, KS 66201.

640D/F

MISSOURI

Anesthesiologist BC/BE needed for MD/CRNA team in a 370-bed regional referral center. No OB. Competitive salary and benefits. Please send resume to 210 East Weaver Road, Springfield, MO 65810. (417) 882-5555.

641D

MOUNTAIN SOUTHWEST

Anesthesia care team in level II trauma center seeks anesthesiologists and CRNAs for full-time and part-time positions. Reply in confidence to Box 642D/F.

642D/F

MAINE

Anesthesiologist needed to join five-anesthesiologists, 10-CRNA group doing wide range of surgeries at two community hospitals. No open heart. Picturesque central Maine location near lakes, mountains, and ocean. Referral area of 75,000+. Competitive compensation package. Contact Jill Gilbert at (207) 872-1136 or send CV to Waterville Anesthesia Associates, 44 Main Street, Waterville, ME 04901.

643D/G

CALIFORNIA

Santa Clara Valley Medical Center, a 600-bed acute care hospital, affiliated with The Stanford University Medical School, is seeking BC/BE anesthesiologists to fill an expanding all-physician department. Competitive salary and fringe benefits commensurate with training and experience. Interested parties should send their CV and the names of three references to James B. Patka, MD, Chairman, Department of Anesthesiology, Santa Clara Valley Medical Center, 751 South Bascom Avenue, San Jose, CA 95118.

644D

MICHIGAN

Expanding surgery load results in opening of attractive permanent position for BC/BE "Team Player" in four-person fee-for-service practice in friendly four-season recreational, lakeside community. Share call and 3800 cases annually at 174-bed hospital. Little OB, no OH or Neuro. Send inquiries and CV to Stephanie Riemer, Mercy Hospital, 400 Hobart Street, Cadillac, MI 49601, or call (616) 779-7404.

645D/F

ANESTHESIOLOGIST

Excellent opportunity for BC anesthesiologist or BE if resident. University-affiliated teaching hospital. Quality, responsive, cohesive medical staff. General anesthesiology, some neuro, no hearts. 80%–90% same-day surgeries. Adding new OB service. Must be comfortable working with CRNAs and have excellent communication and technical skills. Call 1:6. Excellent compensation, incentive, and benefits. Midwestern city with quality lifestyle and outstanding recreational activities. For details send CV or call Carol Paule, Cejka & Co., 222 South Central, Suite 700, St. Louis, MO 63105; 1-800-765-3055.

651D

ANESTHESIOLOGIST

Department of Anesthesiology at the SUNY Health Science Center in Syracuse, N.Y. is recruiting faculty at the instructor and assistant and associate professor levels. Qualified individuals with a strong academic commitment in all types of anesthesia, critical care, and pain management are sought. SUNY Health Science Center is a tertiary care center and provides clinical services also to the Syracuse Veterans Administration Hospital. Rank and salary are commensurate with experience. Must be board certified or board eligible and possess a New York State medical license. Please send letter, curriculum vitae, names, addresses, and phone numbers of three references to Enrico M. Camporesi, MD, Professor and Chairman, Department of Anesthesiology, SUNY Health Science Center, Syracuse, N.Y. 13210. The State University of New York Health Science Center is an Equal Opportunity/AA employer.

652D/F

Anesthesiologist with experience and expertise in acute and chronic pain management is sought to establish a pain management service for both inpatients and outpatients. Ours is a large group practice in the mountains of the southeastern U.S. Compensation and benefits will be commensurate with training, experience, and board certification. Reply to Box 653D/G.

653D/G

CALIFORNIA

The UCLA Department of Anesthesiology is searching for a faculty person with experience in ophthalmologic anesthesia to be Chief of the Ophthalmologic Anesthesia

Division. Candidates are required to show evidence or promise of research productivity and scholarly writing. Other requisites include clinical and teaching skills, commitment to discovery, eligibility for a California medical license, ABA certification. Address correspondence with names of five references and curriculum vitae to Thomas M. Grove, MD, PhD, Department of Anesthesiology, UCLA School of Medicine, Los Angeles, CA 90024-1778. UCLA is an Affirmative Action, Equal Opportunity Employer.

654D/F

NEW YORK
Board-certified or board-eligible anesthesiologist with clinical, teaching, and research capabilities needed for a university-affiliated VA Medical Center. All types of surgery except neuro and obstetrics. Salary based on experience. Federal fringe benefits package. Please contact by phone or send CV to Personnel Service, VA Medical Center, 3495 Bailey Avenue, Buffalo, NY 14215; (716) 862-3643. Equal Opportunity Employer. Applicants are subject to random drug testing.

655D

ILLINOIS
Anesthesiologist BC/BE sought for MD/CRNA team at progressive 350-bed southern Illinois hospital which includes cardiothoracic. CV to Box 587AC.

587ACD

PAIN MANAGEMENT
Excellent position for BE/BC anesthesiologist with pain management fellowship or experience. Excellent pay, no call, no weekends, 7–5 job, OR coverage available. Wonderful "cajun city," close to New Orleans and Houston. Early partnership. Great financial potential. 1-318-468-4016.

656DE

UNIVERSITY OF PENNSYLVANIA
Anesthesiology Research Training: Applications are invited for 2 years full time in an NIH funded, Training for Anesthesia Research program. The specific program (and areas of training) is individually designed to meet the needs of each trainee and is usually a mix of course work and laboratory or clinical research activities. The research training is coordinated between the Department of Anesthesia and the chosen basic science field. For information write (include current CV) to Bryan E. Marshall, MD, FRCP, Director, Training for Anesthesia Research Program, 781 Dulles, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104.

657D/F

DANIEL & YEAGER LOCUM TENENS
Daniel & Yeager is the only name you need for locum tenens. Anesthesia is our exclusive specialty, so you are assured of our undivided attention. Earn a premium income while eliminating administrative headaches and malpractice premiums, we cover it all. Call 1-800-955-1919 or write to PO Box 2065, Huntsville, AL 35804-2065.

629C/H

LOCUM TENENS
Locum tenens anesthesiologists. Earn up to $200,000.00 per year. Don't work for an agency. Work for yourself. For details, send name and address to Dr. Monroe, 7035 Hwy 6 South, Suite #175-B, Houston, TX 77083.

616C/F

TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:
The unique feature of these tutorials is the small group size. The personalized format with a maximum of four students in a session allows your performance to be evaluated throughout the session and permits you to raise questions for discussion. Tutoring for the written and oral exams are given separately. The sessions are held in San Francisco and New York and are given in blocks of 3 days. FOR THE WRITTENS, essential test-taking skills are taught for dealing with multiple-choice questions. The basic sciences are stressed. FOR THE ORALS, mock orals are practiced using the guided case discussions which meet the Board's stated objectives. All students will receive study programs for use following these sessions. CALL 415-321-1117.

628C/H

J. STEPHENS MAYHUGH AND ASSOCIATES LOCUM TENENS ANESTHESIA SERVICES
Providing top-quality CRNAs to meet your specific needs. Our CRNAs are screened to assure quality in performance as well as personal stability. License verification, curriculum vitae, references procured by us, AANA recertification, malpractice verification are supplied to you. Call 1-800-426-2349 any time.

552L/E

DON'T FAIL THE WRITTEN BOARDS/ITE
New 1991 edition of practice questions (including past board remembered questions), answers, test-taking techniques, and more. We want to help you pass. Order the original, MEDTEXT call 1-800-695-6301 24 hours a day.

590A/F

(800) FAST-GAS
The number that hundreds of hospitals nationwide have called for permanent and temporary anesthesia services. The number that thousands of anesthesia professionals have called to secure permanent and temporary positions nationwide. Bay Area Anesthesia, Inc. 1-800-327-8427 for years of professional anesthesia service.

582B/G

Dial 1-800/RENT-A-DOC
For anesthesiologists and CRNAs. We can provide you with quality locum tenens services to meet your specific coverage needs. Or work locum tenens with us for a change in both your practice and your lifestyle. ReplaceMed * 1-0800/736-8236 * PO Box 640 * Michigan City, IN 46360.

598B/L

A WEEKEND OF PRACTICE ORAL EXAMS
Practice exams, not lectures. We are the original course in this format. 20 hours Category I CME credit, two board-certified instructors, 12 students maximum. Dallas, June 28–30. Call for later class dates in Denver, Detroit, and Tampa. ANESTHESIA EXAM REVIEW, 7128 Regents Park, Toledo, OH 43617 (419) 843-4480 or (813) 394-8780.

646DE

INDEX TO ADVERTISERS

Anaquest
  Stadol .... A31 thru A32

Augustine Medical
  Bair Hugger A6

Burroughs Wellcome Co.
  Tracrium .... A26 thru A28

Columbia University at Harlem
  Recruitment A34

Drug Free America
  Corporate A30

Franciscan Children's Hospital
  Recruitment A34

Guthrie Clinic
  Recruitment A34

Janssen Pharmaceutica
  Alfenta .... Cover 4
  Sufenta A4

Medtronic, Inc.
  SynchroMed .... A13 thru A14

Montefiore Medical Center
  Review Course A25

Northern Health Systems
  Computer Systems A29

Ohmeda
  Rascal II A16

Organon Pharmaceuticals
  Arduan .... A37 thru A38
  Norcuron .... Cover 2 thru A1

Osler Institute
  Courses A24, A35

Preferred Physicians Mutual
  Insurance .... Cover 3

Professional Seminars, Inc.
  Seminar A25

Hoffman La Roche
  Versed .... A10 thru A12, A41 thru A42

Stuart Pharmaceuticals
  Diprivan .... A17 thru A23

Advertising Office: Pharmaceutical Media, Inc., 440 Park Avenue South, 14th Floor, New York, New York 10016. Telephone: (212) 685-5010

ANESTHESIOLOGISTS

CHOSEN BY MORE ANESTHESIOLOGISTS THAN ANY OTHER COMPANY IN THE NATION.

Malpractice insurance exclusively
for selected anesthesiologists.

**PREFERRED
PHYSICIANS
MUTUAL**
Risk Retention Group

Preferred Physicians Mutual
204 Lucas Place
323 West 8th Street
Kansas City, Missouri 64105
Call Toll-free 800-562-5589

FOR SHORTER SURGICAL PROCEDURES:
THE ALFENTA ADVANTAGE

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.

Rapid-acting

Alfenta®
(alfentanil HCl) Injection CII

For moment-to-moment control of stress responses

RAPID ONSET
Rapidly blocks sympathetic responses to induction and intubation

SHORT DURATION
Results in quick recovery of consciousness*

RAPID RECOVERY
Postoperative respiratory depression is of short duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 μg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE. BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 μg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 μg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to ¼ of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 μg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 μg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at leas 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO_2. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 μg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and nondisturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD_{50} of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSAGE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854

March 1987, April 1988
U.S. Patent No. 4,167,574
49-7619902-M

© Janssen Pharmaceutica Inc. 1989 JPI-AL-040A